The New England
Journal of Medicine

Copyright, 1948, by the Massachusetts Medical Society

Volume 239 DECEMBER 23, 1948 Number 26

MORAL PROBLEMS IN THE PRACTICE OF MEDICINE*

With Analogies Drawn from the Profession of the Ministry

WILLARD L. SPERRY, M.A., D.D., S.T.D., AND LITT.D.†

CAMBRIDGE, MASSACHUSETTS

MAY I begin what I have to say to you this afternoon by thanking Dr. Means for his kind invitation to me to share your staff meeting with you. And may I add my thanks to all of you for your co-operation in the Institute of Pastoral Care, which heads up at the Massachusetts General Hospital.

The fact that I am here at all and that this institute is centered at your hospital is symptomatic of one of the most significant facts in our life today — the fact that, as in the natural sciences, so in the sciences of man and in the professions, the party walls between fields of specialization are not so high as they once were. When I began my ministry I kept bachelor's hall with a well known surgeon. Occasionally I went his rounds with him. One night he routed me out to go along with him to a hospital. He was giving oxygen to a dying patient. As we came out of the room he said, "She'll be gone before morning." I asked, "What happens to her then?" He replied, "That is your business, not mine. You and I are never in the sick room at the same time. We meet at the doorway. You come in as I go out." That would hardly be said today. Our professions may not coincide, but they do overlap.

May I continue by saying that the standards of your profession are, on the whole, higher than those of any of the other professions. I say this without disparagement of the earnestness and the devotion of the members of my own profession. But the separation of church and state in America forbids the state to do anything whatsoever to maintain decent minimal standards for the ministry, whereas the Commonwealth can and does require of you an adequate education before you may practice medicine. Not only so, but your own professional ethics, over and above the competence required by law, maintain your usage at a very high level. Take a single instance. A professional man is not supposed to advertise. If the newspapers carried, day by day, medical parallels to the advertisements run by the churches on a Saturday and the publicity that ministers allow themselves on Monday, any doctor who sanctioned such self-advertisement would find himself charged at once with unprofessional conduct. I do not hesitate, in dealing with students in the Divinity School, to call attention to the high ethical standards that prevail in the field of medicine.

I have been asked by Dr. Means to talk about certain problems that we share together — problems that are more properly moral rather than medical. We shall come to cases a little later on. But I have to warn you, as I warned him in accepting his invitation, that these problems have no single, simple solution. However, Havelock Ellis once said that the important thing is not to find a man who knows the answer to your problem, but to find a man who knows what the problem is. Were I minded to do so I could cite problems in the practice of my own profession that are, in principle, substantially those which Dr. Means had in mind in inviting me here. I merely ask you to take it for granted that I am not wholly unfamiliar with the type of situation that you face.

When we talk about morals and ethics we may mean one of two things. The two words mean, linguistically, the same thing — the *mores* or the *ethos* of a society; that is, the mean high-water mark of accepted manners in a given society. Thus a recent *Handbook of Psychiatry* (Overholser and Richmond) says, "Conscience is not something that is born in the individual, but something that is acquired from the practices, the beliefs, the attitudes and the customs of the group with which the individual identifies himself. For the average individual his conscience is the crystallized attitude of his group." This is a purely naturalistic, sociologic account of morals. It makes large room for relativity in the whole field of ethics, and for the changes in moral standards of which all of us are aware.

On the other hand there are persons, and these in the main professedly religious persons, who are not content to define and dismiss morality as a

*Presented at a staff meeting of the Massachusetts General Hospital, Boston, January 19, 1948.

†Dean, Harvard Divinity School.

matter of social custom. Such persons feel that the distinction between right and wrong, in whatever terms these two words may be defined, has about it a certain absolute quality. Thomas Carlyle says that the greatest moment in modern European history was that when a lonely man stood before a hostile court and said, "It is dangerous to sin against conscience." Most of us have had moments in which we were aware of that danger. In the ancient Wisdom Literature of Israel there is a verse in which God says, "Thou hast not as it were forsaken me, thou hast forsaken thyself." To "forsake oneself" is a serious business; the process may eventually become suicidal for character.

Therefore, I commend to you another account of morals by Father George Tyrrell:

> The rock of irresistible reality is conscience — the sense of right and its absolute claims. No analysis, no explaining away can permanently destroy this faith or lay the ghost. Only conscience can say, "Thou shalt have no other gods before me; thou shalt not bow down to them or worship them, for I the Lord thy God am a jealous God."

The sciences of man can prove beyond all contradiction the relativity of moral judgments at any given place and time. A practice that yesterday was declared to be permissible, if not right, is today declared to be forbidden and wrong. Polygamy and human slavery are two historic instances of this proposition. The prodigal varieties of moral judgment, and the fact, which each one of us has verified in his own experience, that conscience is educable, inclines the sociologist to regard the whole matter as one of ethical relativity. But the religious man cannot abandon altogether his conviction that, whatever its particular pronouncement at any given moment, the principle of conscience has an absolute warrant. No rationalization can explain, much less explain away, this conviction, which has its origins in the belief that the life of man is lived in touch with an "Infinite Mystery" and that our attempts to distinguish between right and wrong have their ultimate origins in the nature of "The Eternal Goodness." The process of ethical culture still goes on, but the quality of an ethical conviction remains constant.

To come more closely to our immediate subject: the actual moral choices that we have to make in this world are seldom between black and white; they are between shades of gray. One of my friends, who taught the undergraduate classes in ethics at Yale, used to say that once we have chosen the lighter shade of gray, we must then, for all practical purposes, go ahead on the assumption that it becomes for us a clear white.

The narrator in Conrad's *Lord Jim* says of his tragic hero that, given his dilemma, there was only a hairbreadth, only the thickness of a sheet of paper, between right and wrong. Once again all of us have had experience of this narrow margin between our moral options.

The most serious and by far the most difficult moral decisions we have to make are those that involve two rival loyalties, each of which is wholly good on its own premises, but which cannot be easily squared. I cited you a moment ago Father George Tyrrell. There is in his autobiography a poignant passage that harks back to just such a collision of loyalties in his own early life. He had felt a call to the religious life and had decided to join a religious order. But his decision meant abandoning to their own fate a needy mother and sister who, humanly speaking, had simple prior claims upon him. Looking back on his decision he said years later:

> Well I remember my last day at home, my last day with those two now hid in death's dateless night, who were my share of the world, the best this life has had for me — whom I forsook for what? in the name of all that is sane and reasonable? For a craze, an idea, a fanaticism? Or for the love of and zeal for the truth, the Kingdom of God, the good of mankind. Had I been faithful to my duty all along, had I stayed at home and supported my mother and sister and made their sad narrow lives a little wider and brighter, would not God have given me light needful for my salvation? Have I done so much good to others who had no claim on me to atone for my neglect of those who had every claim? What have I given up or forsaken for the service of God, as I suppose some would call it, except my plain duty? These are the pleasant doubts that fill my mind in the spare moments, and make me say, Surely I have lived in vain.

In his *Oxford Lectures on Poetry*, A. C. Bradley has an essay on "Hegel's Theory of Tragedy." He points out that tragedy is never a matter of a conflict between good and evil. Such a conflict is forthright and never tragic. The essence of tragedy is, as we have said, a matter of a collision of two loyalties, each of which is wholly good on its own ground:

> The essentially tragic fact is the self-division and intestinal warfare of the ethical substance, not so much the war of good with evil as the war of good with good. . . . The family claims what the state refuses, love requires what honor forbids. The competing forces are both in themselves rightful, and so far the claim of each is equally justified, but the right of each is pushed into a wrong because it ignores the right of the other.

Professor Bradley illustrates this thesis at great length from the great Greek tragedies and from those of Shakespeare. Clytemnestra has killed her husband and her king. Orestes, her son, is ordered by Apollo to avenge his father, but to kill one's mother is itself a sin against filial piety. The bond of father and son demands that which the bond of son and mother forbids. Richard Lovelace, on going to the wars, says to his *Lucasta*:

> Yet this inconstancy is such
> As you shall too adore;
> I could not love thee, dear, so much,
> Loved I not honour more.

This was Othello's tragedy: his passionate love of Desdemona and his duty to his honor were at the final fatal moment incompatible, so he "put out the light."

The essence of tragedy, then, is not pain or suffering. The essence of tragedy is waste. We are confronted again and again with what William James has called "a forced, momentous option." This option cannot be avoided; a choice must be made, but when it is made something good in itself is inevitably lost.

In this analysis of our moral problems we come here to an area of life where crude rules of thumb, which serve the humdrum needs of every day, are of little help. We must go to art, and perhaps to religion, to understand the nature of our dilemma and to find there some element of resignation and reconciliation.

To come to still closer grips with our problem let me take two or three instances of the tragic dilemma with which we are only too familiar. At these points the professions of medicine and the ministry constantly overlap. Please understand that what I may say hereafter provides no dogmatic resolution of the tragic dilemma. I offer merely my own reflections upon situations that are even more familiar to you than they are to me, and yet situations that, over the years, I have shared with you. For there are times when a patient asks a priest or minister or rabbi questions that he shrinks from asking his doctor.

Telling the Patient the Truth

This issue was, you remember, one that was vigorously debated here in these very circles some years ago, when a gallantly and remorselessly sincere man urged truth telling at all costs.

One might dodge the issue by asking in turn, with Pilate of old, "What is truth?" Bacon said that Pilate was merely a jester, who would not stay for an answer. My observation is that many wise physicians and surgeons are cautious about claiming finality for their diagnoses and prognoses. In the order of nature there are run-of-the-mill diseases that, humanly speaking, must apparently go their normal course to the end. It is a matter of common knowledge that the faith-healing sects in this country have made much of their capital out of hasty and erroneous diagnoses. Some would-be truth teller, who misinterpreted the facts, has dismissed them, perhaps to the ministry of devout believers, but certainly to the *vis medicatrix naturae*. This, however, is more immediately your problem than mine. Furthermore, as one of you said to me not long ago, we never know when some new treatment and possible cure may come suddenly around a corner. Years ago a little daughter of Dean Inge of St. Paul's and a son of L. P. Jacks were taken to London hospitals in the last stages of diabetes, to await the first insulin that was being flown to England from Canada. The girl, alas, died; the lad lived to get his insulin and still lives happily.

But when there is reasonable assurance as to diagnosis and prognosis, what are the doctor, and the minister who shares the doctor's opinion, to do?

Much, perhaps all, depends on a patient's temperament and mental state at the time. Resolute natures, in full possession of their wits, usually want to know what we think and expect, and are able to "take it." I see no reason or warrant for withholding what we believe to be the truth from such a person. I mentioned that Yale professor a few moments ago. He had an obscure illness and died untimely, after going the rounds of specialists in both New York and Boston. He was a man of quick intellect and good courage. He once said to me, in a mood of discouragement and temporary bitterness, "I no longer believe anything that any doctor says to me. They have all lied to me so consistently that I have lost all faith in them." This was a bit of deliberate overstatement on his part, but I think he meant that he was tired of being cheered up by a too facile optimism, or dismissed with deliberate perplexity.

On the other hand many persons do not even ask themselves how ill they are, let alone asking any one else. They prefer to take what comes, as it comes. The reticence of such persons should be respected. There is no occasion and no moral obligation to intrude the supposed truth upon such minds. To do so would be a bit of gratuitous cruelty. And all of us know that there is a point in the course of an illness at which nature herself mercifully dulls the mind and its power of grasping ideas begins to relax. In his Ingersoll Lecture on the Immortality of Man, given at Harvard some years ago, William Osler said that most people die as they were born, unconscious of what is happening. You doctors know this well. I have to tell my divinity students that this is so, and that at these times they are not to ask or expect anything like quick mental response to their ministry to the sick. These are not the occasions to carry on a prolonged discussion as to an afterlife.

In short this whole question of truth telling seems to me to depend upon the temperament and the mental state of a patient. No single categorical rule can be laid down; we have to trust our instinctive knowledge of human beings and be guided accordingly.

Prolongation of Life and Euthanasia

Regarding the first of these questions there seems to be little question. There is a point beyond which the mere artificial prolongation of the life of a body that seems marked down for death is not merely useless but also even an unkindness. One might even defend the thesis that it is a perverted conception of goodness and of ethics. When Shakespeare says, "She should have died hereafter," he meant, not that her death was premature, but rather that she was going to die some time and in any case.

When we are actually in sight of that time it seems to be right to accept the fact. I have never come across on the part of the laity any difference of opinion about the medical conduct of a case once this situation is accepted.

The question of euthanasia is more difficult. There is, as you know, much vocal medical opinion in its favor in England. And the matter is often discussed privately here. It is an open question. As to the act itself, many a suffering person has begged for it, many kinsfolk have been willing to accept it, and I suspect that many a doctor has been sorely tempted at this point. I have a friend who, with the connivance of her doctor, gave her husband, who was suffering from a cruelly painful and fatal disease, a heavy overdose of morphine. She said she had no scruples about doing so and had never had a single regret. You must know many more such examples than I know. She was either more resolute or more fortunate than most human beings. A few years ago I watched my Scottish terrier being put away. He was old and blind and sick. But even so I didn't like it. It seemed to me that the veterinarian and I were taking a great responsibility and one perhaps to which we were not morally entitled. How much more so in the case of a human life!

If euthanasia were ever to be legalized no single medical man could be or should be empowered to make such a decision alone. A panel of doctors would probably have to be set up by the state to make any such decision. Public medicine of any kind raises all sorts of valid questions. It is not easy to foresee a panel of state officials charged with this task, nor is it easy to envisage the doctor who would accept this responsibility as the major, if not the sole, form in which he practiced his profession. Whatever the warrant of a given emergency may be, the legal validation of euthanasia seems to cut against the whole basis and practice of medicine. I suppose that none of us are 100 per cent psychologically sound, and one wonders what perversions might creep into the practice of euthanasia.

Albert Schweitzer, who is a doctor as well as a minister, and who has done such splendid work at Lambarene in West Africa, says of himself that journeying up river from the coast to his hospital on one occasion he was searching for some basic ethical principle:

> Slowly we kept upstream, laboriously feeling for channels between the sand banks. Lost in thought I struggled to find the elementary and universal conception of the ethical which I had not discovered in any philosophy. Sheet after sheet I covered with disconnected sentences. Late on the third day at the very moment we were making our way through a herd of hippopotamuses, there flashed upon my mind, unforeseen and unsought, the phrase "Reverence for life." For all life.

His autobiography has many striking instances of his subsequent application of that principle.

This is, after all, the ethical basis of the practice of your profession as of my profession. If we forfeit that reverence we have slipped our moral moorings. And if in practice we violate that principle, we should know that we are doing so and take the responsibility for so doing. Once again, "Thou hast not as it were forsaken me, thou hast forsaken thyself." To forsake one's own self is an act that leaves its scars on the mind. Personally, I should question the wisdom of medicine's accepting as a principle, and the state's legalizing in practice, acts of euthanasia. Such a *volte face* in the whole conception of the aim of the profession would impair the conscious integrity of its members and would introduce in place of an accepted principle — which, if it is ever to be violated, should be violated soberly and wittingly — a state of ethical perplexity and painful indecision in which each case must be decided on its own merits. The effect on the public would be almost disastrous, since it would introduce into these relationships a sense of insecurity and apprehension, rather than confidence and assurance. If a doctor or a minister has never had, or having had has lost, his reverence for life and his feeling for the sacredness of life, he lacks that which in theory his profession presupposes. Unless you and I are to revise radically our conception of our common task, it is not our business to take life, only to try to save it.

Rival Claims of Competing Individuals, or of the Concrete Individual and Society in the Abstract

We come, finally, to the specific type of problem that was proposed to me. Here is a woman apparently dying of an inoperable and incurable cancer of the stomach. She is being kept alive by blood transfusions, but the blood that she needs is the rarest type, of which the blood bank has only a limited supply. The transfusions cannot save her. Is it not foolish, perhaps even wrong, to waste this precious blood on her? Ought it not to be kept for some later patient who may be helped by it, whose life perhaps may actually be saved by it? Or here is a man in the iron lung, who could not live an hour outside it and yet may live half a lifetime in it, to the exclusion of someone else who might be got around a bad corner and in due time dismissed. Ought he to be allowed his monopoly of this mechanism?

These are difficult, even heartbreaking questions. Either way, the choice is a genuinely tragic one. I do not know that I have sufficient wisdom to answer them. I can only fall back on general principles.

There are two terms that have been much to the front in recent years. They represent what are called social trends. One is the word "depersonification," and the other the words "mass man." Both terms represent tendencies, particularly on the part of the state, to depreciate the value of the

single individual in favor of the group as a whole. These trends have found their fullest expression in countries where totalitarianism has been, or still is, the order of the day. In such societies the individual is of value only as a member of the mass, and is always regarded as expendable.

Our own country has just now fought two world wars in defense of the general idea of liberty and the rights of the individual. His liberties have had to be circumscribed in wartime, and now that the fighting is for the moment over, we are left with lives that are much less free, as far as our private affairs are concerned, than they were forty years ago. It could not have been otherwise, perhaps, and yet this steadily narrowing area in which anything like actual liberty and private initiative remains is one of the paradoxes of these years.

There is abroad a tendency to treat this doctrine of mass man as though it were a late discovery, the mature achievement of complex modern societies. I venture to point out that, on the whole, it is the oldest of all our social theories. It was the appraisal of life current in all primitive societies. The individual mattered only as a member of the tribe, and all the tribal rites looked to his initiation into the tribe and his subsequent identification with it. This was true of the religion of the early Israelites. The single individual had no independent worth either in his own eyes or for his fellows or even to Jehovah. The doctrine of the worth and moral independence of the individual emerges only with the prophet Ezekiel after the return from the exile. This lead is taken up and matured in Christianity, which holds that "not a sparrow falls to the ground without your Father." However difficult the doctrine may be to understand and defend, such is the doctrine of later Judaism and Christianity — both have traditionally believed in the value of the individual. Our social institutions come into being to express him and to defend him. "The Sabbath was made for man, not man for the Sabbath."

This appraisal of the facts was, also, the premise of all modern democracies, our own in particular. The case has never been theoretically proved beyond all contradiction, or vindicated in the total practice of any society. It remains, in many respects, a bold ideal. But unless we repudiate our hereditary faith, both religious and political, it is still our ideal, and its denial would mean a radical change in the whole temper of our life.

The drift of the times, in the worlds of finance and industry, and in military policy, seems to be in the direction of the dogma of mass man. At their hands the individual is inevitably more or less depersonalized. Perhaps it cannot be otherwise, given the numbers of human beings involved and the complexity of most modern issues.

In any case it is left largely to two groups of professional persons, the doctor and the minister, to vindicate a working faith in the value of the individual. Any lack of that faith on our part is tantamount to desertion of an ideal outpost that we have held in behalf of what we believed to be a valid cause.

The first social-settlement house in the English-speaking world, Toynbee Hall in East London, was presided over by a quiet little Anglican clergyman, Samuel Barnett. In her biography of her husband Mrs. Barnett says that any number of persons used to come down for a day from the West End of London to its dreary East End, with large blue-print plans for the redemption of those drab slums. They aired their plans, spent a pleasant evening with the warden and went away. Mrs. Barnett says that her husband came to the conclusion that the only permanent good ever done in the East End of London was done by those "who were willing to take time and trouble with individuals," and that this verdict upon the fact became his own rule of life.

A man who goes into the practice of medicine or of the ministry ought to enter his profession with that conviction and ought to do his best to vindicate it. There is a place in society for the man who wishes to devote his life to the general and all-over cause of public health. There is a place in the religious world for a man who feels he should sign on with one or another of the great reform movements of the time. The work of these men is necessary, and their contribution to society may be very great. But the practicing doctor and the parish minister are primarily concerned with individual human beings. The moment either begins to sacrifice his concern for the individual to some other hypothetical person, or to society in the abstract, he has mistaken his vocation.

He may justify his decision to himself on the grounds of a higher or broader loyalty, but he will have failed his cause at a point that it is more and more difficult to hold in the modern world. If he ceases taking time and trouble with a given individual on the ground that he can thus be of greater service to someone else he impairs to this extent the confidence of the community in himself and his profession. Once a man accepts the ministry of a parish he is under bonds to take time and trouble with the individuals who comprise it. Most of the failures that I know of in my own profession have been due to a neglect of that premise. If my analogy is valid I should suppose that once a doctor and a hospital have accepted a patient they are under bonds to see the patient through.

I agree that this may involve what will often seem a waste of precious time to no permanent good. But there is something more at stake here than the welfare of the single patient; there is also the confidence of the community in the integrity and single-mindedness of the profession itself. If

that confidence is impaired not merely the good name but also the actual effectiveness of the profession suffers in consequence.

These are tragic choices. And as Bradley says, the essence of tragedy is the fact of waste that it involves. To know them as tragic and to feel their tragedy is perhaps half the battle at the outset. If a man cannot feel these tragedies in medicine and the ministry there is something wrong with him. If he is a sensitive man he will feel them more deeply as the years go on. He will always make his decisions reluctantly and with pain of heart, if not perplexity of mind. But he is the defender in church and state of certain basic principles of our society that he cannot forfeit without radically revising the premises of his profession and to this extent impairing the whole tradition to which he belongs.

* * *

I have not answered Dr. Means's problems, or yours. But I have tried to point out what some of the issues are. In so far as I have any answers they are, briefly:

Tell the truth, but "tell the truth in love," and telling the truth in love may often mean silence rather than some hastily spoken word.

Maintain at all times a sense of the sacredness of life.

Be willing to take time and trouble with individuals at the expense of that abstraction known as mass man.

PROGNOSIS IN ESSENTIAL HYPERTENSION*

Eight-Year Follow-up Study of 430 Patients on Conventional Medical Treatment

ROBERT STERLING PALMER, M.D.,† DOROTHEA LOOFBOUROW, M.D.,‡ AND CARL R. DOERING, M.D.§

BOSTON

CONSCIENTIOUS interval evaluation of sympathectomy for essential hypertension by comparison with control material is progressively defining the limitations and the applicability of this procedure.[1, 2] The same attention to control material is required when one considers the usefulness of very restrictive diets, interest in which has recently revived.[3, 4] Before applying these diets generally and indiscriminately, we should ask ourselves what the remote effects will be on the body electrolyte economy, on work capacity and hot-weather tolerance, on resistance to infection, on the basal metabolism, on carbohydrate tolerance and on fetal health in pregnancy. Finally and practically, how often is an extremely irksome diet necessary in essential hypertension? If employed, does it actually prolong the life of the patient? Are most of the successes obtained in those patients likely to be matched in any case? To help answer these three important questions, adequate control material is the first necessity. This we believe we have and submit it herewith. In this series of cases, treatment consisted of the combination of physical rest and activity deemed appropriate for each patient, sedative drugs and sometimes sulfocyanates, low-fat, relatively high-protein and low-salt diets, in exceptional cases low-sodium diets for short periods, the usual drugs for congestive or anginal failure and finally practical psychotherapy.

Originally, our series of patients with hypertension consisted of 1072 patients personally observed, the great majority of them between 1935 and 1940. After patients with transient nervous hypertension, those with glomerulonephritis, those who were sympathectomized and those inadequately followed had been excluded, 646 subjects remained. Observation comprised a careful history and physical examination, routine blood and urine examinations, a fractional intravenous phenolsulphonephthalein test, a urine concentration test, frequently intravenous urography or orthodiagram or seven-foot film of the heart and an electrocardiogram.

After the original observations and satisfactory follow-up study, these 646 patients were classified according to clinically recognizable organic changes in the three vital areas: the head, the heart and the kidneys. The classification depended upon the most marked change in the area or areas in which it was found. These criteria are presented below.

CLASSIFICATION

Grade I Changes

These patients have no changes or minimal changes in the fundi as represented by narrowing

*From the Committee on Research in Diseases of the Autonomic Nervous System, Massachusetts General Hospital, and the Harvard School of Public Health.

This study was supported by a grant from the Life Insurance Fund of America.

†Associate physician, Massachusetts General Hospital; consulting physician, Massachusetts Eye and Ear Infirmary.

‡Assistant in medicine, Massachusetts General Hospital.

§Assistant professor of biostatistics, Harvard School of Public Health; consultant, Cambridge Tuberculosis and Health Association.

of the arterioles, normal hearts or no more than prominence in the region of the left ventricle by x-ray study, no impairment of renal function by the tests used and normal urine examination or occasionally slight albuminuria and slight changes on microscopical examination of the sediment.

Grade II Changes

These cases include moderate organic changes in the fundi as represented by widening of the arteriolar light reflex, narrowing, caliber changes and arteriovenous compression. The heart exceptionally is normal by x-ray study and is usually prominent in the region of the left ventricle and sometimes more definitely enlarged but without functional impairment; the kidney is normal, slight degrees of albumin and minimal numbers of formed elements are found in the sediment, or there may be slightly impaired function.

Grade III Changes

The fundi are rarely normal, usually showing arteriolar narrowing, caliber changes, wide light reflex and arteriovenous compression. Often, there are exudates and hemorrhages; the heart is often moderately to markedly enlarged, commonly with symptoms and signs of actual or impending congestive failure or symptoms of anginal failure. The urine frequently shows albuminuria and casts, and renal function is often impaired though actual failure (uremia) is not common; cerebral accidents sometimes occur (in 20 per cent of cases).

Grade IV Changes

The cardinal — indeed, the obligatory — sign is edema of the optic disks, with or without exudates and hemorrhages and always with marked narrowing of the arterioles. Cardiac enlargement and congestive failure may be present; renal impairment and failure are common.

It is emphasized again that classification is not based on one organ, such as the fundus, but on recognized changes in any area, and that the classification is: mild (Grade I), moderate (Grade II), or severe benign (Grade III), according to the most advanced change, whether in one or more areas. For instance, a patient who has had a cerebral thrombosis is placed in Grade III, though the heart, kidneys and fundi are normal; no classification higher than III is made if the kidneys are impaired, there is angina pectoris, and there are exudates and hemorrhages in the eyegrounds — that is, there may or may not be evidence that one or all vital areas are affected seriously. Grade IV or malignant hypertension is recognized by papilledema alone with or without other changes. In 95 per cent this sign indicates a rapidly progressive course to a fatal outcome. In Grades I and II patients must be observed a year or more for one to be sure that the course characteristically is progressing slowly, if at all. In Grade III serious change is promptly recognized in fundi (exudate or hemorrhages, or both), in the cerebral circulation (thrombosis or hemorrhage), in the heart (marked enlargement, actual or impending congestive or anginal failure) and in the kidneys (significant impairment of function).

We are well aware that the outward signs are poorly correlated with the inward state in essential hypertension as in other aspects of man, but we must use the signs that we have. For this reason, any clinically observable sign of vascular change in one or more of the three vital areas is taken as indicative of diffuse vascular disease, however localized such a change may be on clinical examination. It is further assumed that the severity of recognizable organic change as defined in the classification is directly proportional to the severity of the disease process. The latter assumption in practice has proved fairly correct.

In 1942–1943, after an average four years of follow-up study of 50 per cent of the 646 cases, the mortality was 6 per cent in Grade I hypertension, 17 per cent in Grade II, 36 per cent in Grade III, and 80 per cent in Grade IV.[1] In 1946–1947, after another four years, 430 cases, or 66.5 per cent of the 646, were followed. The mortality was 22 per cent in Grade I, 47 per cent in Grade II, 78 per cent in Grade III and 94 per cent in Grade IV. It is evident that this clinical classification of essential hypertension on the average indicates the severity of the disease in respect to survival.

The average and median duration of known hypertension in each grade of the 430 patients is given in Table 1. The known duration of hypertension in Grades I to III is longer in the living (twelve to fifteen years) than in the dead (seven to nine years) patients. This reminds us of three things: that the actual onset of hypertension is hardly ever accurately determined; that the prognosis varies with age and sex; and that present methods of clinical examination as employed by us differentiate patients who do well from those who do badly only by an average of each grade and not in an individual patient. In Grade IV hypertension 3 patients with papilledema have survived an average of nine years and two months. These cases are exceptional. Others have had a similar experience.[5, 6] The average duration in patients with Grade IV changes who died is three and one-fourth years, owing to the long duration of apparently benign hypertension terminated by the malignant phase in some of these cases. The median known duration is just under one and a half years. The average duration of our own observation of these patients is a little over seven months, and the median slightly more than four months. It is almost always apparent at once that the course of the disease in patients with Grade IV changes is intense and rapid. It is usually apparent in Grade

III that one is observing an end stage of a condition that has often been very slowly progressive. In Grades I and II a number of interval observations of a year or more are needed to prove that the condition is slowly progressive or stationary. We know of no infallible signs at a single examination in these patients with Grade I and II changes that will foretell the appearance of late Grade III or malignant Grade IV changes.

The age distribution of the various grades is shown in Figure 1. By inspection, one can notice that the patients with Grade IV changes are younger than all the others and that those with Grade II and III changes are older than those with Grade I. This suggests that Grade I, II, and III changes form a group of patients that represents a condition different from that of Grade IV.

Table 2 shows the sex distribution and survival rates and demonstrates that in this sample there are

TABLE 1. *Average and Median Duration of Known Hypertension by Grades.*

GRADE OF HYPERTENSION	DURATION	
	AVERAGE yr.	MEDIAN yr.
Living patients:		
I	12.5	11.5
II	13.9	13.0
III	14.7	13.0
IV	9.2	—
Dead patients:		
I	9.1	8.5
II	8.6	7.0
III	8.2	7.0
IV	3.2	1.4

more female than male patients with essential hypertension. In Grades I and II the percentage of women is greater than that of men. The reverse is true of Grade IV. In Grade III the numbers are equal, but the percentage of the total number of each sex reveals 50 per cent men and 40 per cent women with this degree of hypertension. In Grade IV the percentage of the total number of each sex reveals 17 per cent men and 9 per cent women. This sex difference is considered significant statistically, suggesting that female patients tend to have the milder grades of this disease. It is an important point also that the probability of survival for females is definitely superior — 82 per cent as compared with 66 per cent for the men in Grade I, and 57 per cent as compared with 42 per cent for the men in Grade II. The probability of survival is somewhat better in Grade III (27 and 17 per cent for female and male patients, respectively) and also better in Grade IV (9 and 3 per cent each for female and male patients).

The onset and progress of organic change in essential hypertension is assumed to depend upon the duration, the persistence and the height of blood pressure. To evaluate the factor of age, the age at first known hypertension was calculated, and Grades I to III were grouped as follows: twenty-nine years or less, thirty to thirty-nine inclusive, forty to forty-nine inclusive, and fifty or over. The mortality and the average duration of known blood pressure were determined for each group. This was not done in Group IV because the course of the disease was short at any age. The results for Grades I to III for the different age groups are shown in

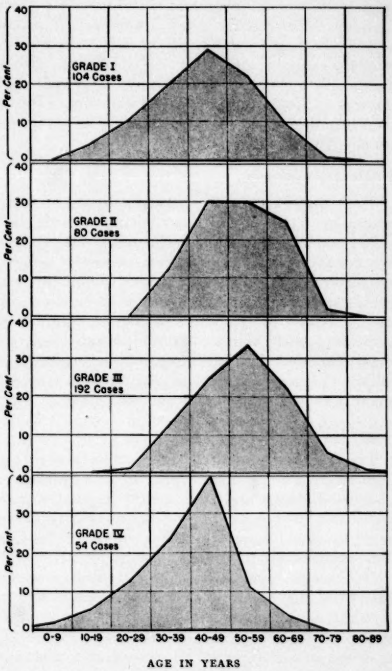


FIGURE 1. *Age Distribution by Decades.*

Table 3. In these mortality figures, deaths from causes other than hypertension are excluded.

From inspection of these figures it appears that an increase in age is associated with a higher mortality only in Grade I hypertension. In Grades II and III the patients are older. The numbers in age group twenty-nine or less are too few to be significant. It is assumed that the course of the disease in many patients in Grades II and III when they were first seen was already more advanced. The usually shorter known duration of hypertension in the dead patients may have been due to the cir-

cumstance that an earlier asymptomatic stage of the disease passed unnoticed. It may be that variations in the natural course of hypertension are due to constitutional, infectious, dietary, situational,

TABLE 2. *Sex Distribution and Survival Rates.*

Grade of Hypertension	Status of Patient	Male Patients		Female Patients	
		no.	survival %	no.	survival %
I	Living	25		56	
	Dead	13		10	
	Totals	38	66	66	82
II	Living	11		31	
	Dead	15		23	
	Totals	26	42	54	57
III	Living	16		26	
	Dead	80		70	
	Totals	96	17	96	27
IV	Living	1		2	
	Dead	31		20	
	Totals	32	3	22	9
All grades	Living	53		115	
	Dead	139		123	
	Totals	192	28	238	48

psychologic or other unknown factors that influence its progress favorably or unfavorably.

We wish to form an estimate of the prognosis of essential hypertension treated by conventional medical management based on the observation of these 430 patients followed in some cases for as long as seventeen years, some of them for shorter

TABLE 3. *Mortality and Average Duration of Hypertension according to Age at Onset.*

Age	Mortality	Average Duration	
		living patients	dead patients
yr.	%	yr.	yr.
Patients with Grade I changes:			
29 or less	12.5	12.5	14.0
30–39	12.0	12.8	9.0
40–49	19.0	11.1	6.2
50 and over	40.0	13.3	9.7
Patients with Grade II changes:			
29 or less	—	20.0*	—
30–39	44.0	15.4	14.1
40–49	48.0	11.4	8.9
50 and over	42.0	11.9	6.6
Patients with Grade III changes:			
29 or less	82.0	—†	11.3
30–39	78.5	15.6	8.7
40–49	68.0	15.8	9.1
50 and over	80.0	11.3	6.9

*Includes only 6 patients.

†Only 2 living patients, both of whom are included under group 30–39 years of age.

periods, the average being eight years, and many of them with known hypertension long before our time of observation. We have taken the 104 Grade I patients, the 80 Grade II patients, the 192 Grade III patients and the 54 Grade IV patients as 100 per cent in each grade and plotted the survival rate in per cent after four years, and again after eight years (Fig. 2). The curve for Grade IV has been drawn with a steeper slope than is apparent from the four-year follow-up study. The reasons for this are that the median duration of known hypertension in this group is about one and a half years and that the median duration of our observation of this group prior to death is only slightly more than four months. If the follow-up examination had been made at two years instead of at four years, we should probably have found just a trifle larger percentage of survivors, as in the patients examined after four years.

Tentatively we have used a method of prediction that is both rough and speculative, by which one

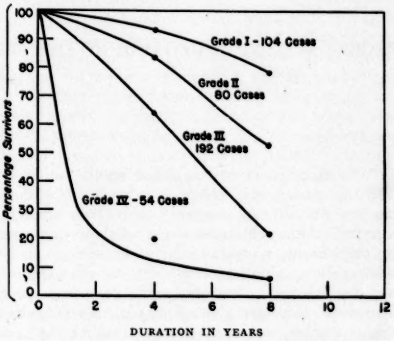


FIGURE 2. *Survival according to Duration of Hypertension.*

might estimate the probable percentage of survivors at twelve years in Grade I as 58 per cent, in Grade II as 24 per cent, in Grade III as less than 2 per cent and in Grade IV as almost zero. Three years hence we hope to have the actual percentages.

DISCUSSION

From our data, the quickest and clearest demonstration of the effectiveness of any therapeutic program will be to show survival of 20 per cent or more of a significant number of patients with Grade IV or malignant hypertension for five or more years. This criterion has been satisfied by Peet's[7, 8] experience with dorsal sympathectomy.

The next most definite criterion of effectiveness of any given program will be to demonstrate the survival of two thirds of a significant number of patients with Grade III hypertension for more than five years.

The therapeutic effectiveness of any program in Grade I and Grade II hypertension will be doubtful until a significant number of patients have been

followed for ten years. At present we may say that considerably more than 80 per cent should be surviving after eight years in Grade I, and 60 per cent or more in Grade II to demonstrate therapeutic superiority. Consideration should be given to the sex incidence in these two grades, and allowance made for the uniformly better prognosis in female patients.

We urge that responsible clinical investigators interested in the study of essential hypertension agree upon terms and criteria for a clinically applicable classification of hypertension for the purpose of establishing the prognosis and the effectiveness of treatment in this, one of the most serious threats to life of civilized man.*

*The classification here used is based on that of Keith, Wagener and Kernohan,[9, 10] whose work in this field since 1920, particularly in establishing the clinical syndrome of malignant hypertension, is gratefully acknowledged.

References

1. Rogers, W. T., and Palmer, R. S. Essential hypertension: prognosis and comparison of medical and surgical treatments. *Am. Practitioner* **1**:459-465, 1947.
2. Palmer, R. S. Medical evaluation of surgical treatment of hypertension. *J. A. M. A.* **134**:9-14, 1947.
3. Kempner, W. Compensation of renal metabolic dysfunction: treatment of kidney disease and hypertensive vascular disease with rice diet. *North Carolina M. J.* **6**:61-72, 1945.
4. Grollman, A., et al. Sodium restriction in diet for hypertension. *J. A. M. A.* **129**:533-537, 1945.
5. Keith, N. M., and Wagener, H. P. Acute vasospastic hypertension: case with signs of cerebral irritation and severe retinitis with remission. *Am. J. M. Sc.* **190**:454-459, 1935.
6. Fishberg, A. M. *Hypertension and Nephritis.* Fourth edition. 779 pp. Philadelphia: Lea & Febiger, 1939. P. 315.
7. Peet, M. M., and Isberg, E. M. Surgical treatment of essential hypertension. *J. A. M. A.* **130**:467-473, 1946.
8. *Idem.* Problem of malignant hypertension and its treatment by splanchnic resection. *Ann. Int. Med.* **28**:755-767, 1948.
9. Keith, N. M., Wagener, H. P., and Barker, N. W. Some different types of essential hypertension: their course and prognosis. *Am J. M. Sc.* **197**:332-343, 1939.
10. Wagener, H. P., and Keith, N. M. Diffuse arteriolar disease with hypertension and associated retinal lesions. *Medicine* **18**:317-430, 1939.

RECENT CONCEPTS REGARDING THE SPREAD AND TREATMENT OF POLIOMYELITIS*

ROBERT B. LAWSON, M.D.†

WINSTON-SALEM, NORTH CAROLINA

THE essential questions asked about poliomyelitis today are, "How is it spread?" "How can you prevent the disease?" and "How can you cure it?" Although the answers to these questions are not known, a vast amount of knowledge about poliomyelitis, which is beginning to fit together, may furnish these answers in the next few years. At present there are glaring gaps in understanding of this disease, but the definite advances that are being made are filling some of these gaps.

Epidemiology

Poliomyelitis is a worldwide disease affecting all races and classes of people. It is recognized to be most important as an epidemic disease, however, in North America, the Scandinavian countries, Great Britain and elsewhere in Europe. Until recently it was assumed to be very uncommon in the other sections of the world. Recent investigations by Paul et al.[1, 2] have shown that, although epidemics of paralytic poliomyelitis are uncommon in the countries of the Middle East and the Far East, nonparalytic and nonepidemic infections are probably widespread in these and similar countries. This was clearly brought out by the experience of British and American troops stationed in the Middle East and Far East respectively. For, although there were only a few cases of poliomyelitis recognized in the native populations, the incidence of poliomyelitis among the foreign military personnel was significantly higher than that in their home countries.

It is noteworthy that recognized epidemics are of recent occurrence and date back little more than sixty years in this country and in Scandinavia. During this period the age incidence of recognized cases has changed. Whereas the disease primarily involved infants and young children at first, there was a gradual extension into the older age groups here and in Scandinavia after the passage of years. Japan, on the other hand, had its first large epidemic in 1939 and, interestingly enough, is having the same younger age incidence that was seen in the early epidemics in the United States. Ninety per cent of the cases reported in Japan were in children under five years of age, whereas only 36 per cent of the patients were under five years in recent epidemics in this country.[1] It seems that there is a higher immunity in the older age groups in these native populations than is apparent in the population of the United States. This can be attributed to a more widespread dissemination of the virus in infancy in these countries, which, with the lower reported incidence of the disease, are also the countries of poor sanitation, so that it has been postulated that poor sanitation leads to wide dissemination of poliomyelitis virus among the young infants, which is not attended with a high rate of paralysis. On the other hand, as a country's sanitation is improved, it seems that more persons escape exposure to the virus in the early years and therefore remain

*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 25, 1948.

From the Department of Pediatrics, Bowman Gray School of Medicine of Wake Forest College.

†Associate professor of pediatrics, Bowman Gray School of Medicine of Wake Forest College.

susceptible to a later and possibly more serious infection.

The spread of poliomyelitis from patient to patient may go on by different routes. It is possible to infect experimental animals and presumably man through three routes: the nose and olfactory bulbs; the skin; and the gastrointestinal tract. It is well accepted that the usual and almost exclusive mode of entry in man is by the oropharynx through the mouth or nose. Virus leaves the human body by two routes, the oropharynx and the lower intestinal tract in the feces. Oropharyngeal swabbings contain virus in as many as 50 per cent of patients, especially for two to three days before the onset of the clinical disease to three to five days after the onset.[3] Stools have been found to contain virus in an even higher percentage of cases, especially in the first two weeks of the disease, but also as long as nineteen days before clinical evidence of infection[4] and six weeks or longer after the onset of disease in some cases.[5] The possible pathways of the virus from the oropharyngeal secretions or feces of the apparently healthy carrier or the clinical case to the new, susceptible person are shown in Figure 1. Virus may be transmitted directly by

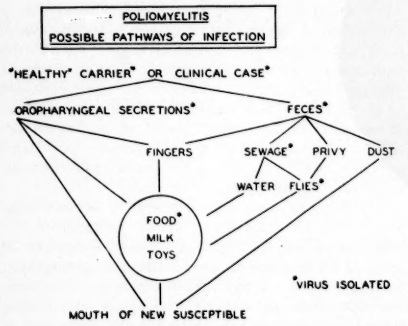


FIGURE 1.

inhalation and ingestion of infected oropharyngeal droplets. Infected oropharyngeal secretions may also be passed by means of fingers and toys or food during the intimate play of children. Fecal virus may be transmitted directly as fecal dust or through the medium of toys among children, just as pinworm ova are spread so widely. Direct fecal contamination of food, including milk, may occur in the same way that typhoid spreads from a carrier, or fecal contamination of food or water may occur indirectly, transported by flies from exposed feces in privies or toilet bowls or from contaminated sewage. All these routes and others are possible and even probable, but there is no agreement on which one is the most important in the actual transmission of the disease. The marked summer incidence of the disease and the finding of the virus in pools of flies caught during epidemics make the theory of fly transmission very attractive. I believe, however, that the fly plays only a minor role.

At present, the most convincing evidence indicates that close contact between human carriers of the virus plays the important role. During any epidemic only a small percentage of people carrying the virus are recognized since the vast majority of carriers do not have a typical illness. There is a serious lack of an easy and economical epidemiologic tool, such as the serologic tests for syphilis or the skin test for tuberculosis, that will pick up these inapparent infections. However, there are several small studies that show the importance of contact. Brown, Francis and Pearson[4] studied a boy's camp in Detroit after the appearance of poliomyelitis in a camper. One week after this case, they found poliomyelitis virus in the throat or feces of 5 of the remaining 7 boys in the same cabin, whereas no virus was found in the 10 boys living in the next cabin. Another interesting point was brought out — namely, that nineteen days later one of these boys carrying the virus developed typical poliomyelitis following severe exertion. A similar study was done by Gear and Mundel[6] in Johannesburg. After the appearance of paralytic poliomyelitis in a two-year-old child they tested the other members of the household and found virus in the stools of an eight-year-old brother. Twelve days later he developed poliomyelitis. Subsequently 2 children whom he had visited just before he became ill developed poliomyelitis, and their father had the virus in his stool. These 3 children and 12 others were at a birthday party together; of this group tests on 8 subjects revealed that 5 were harboring the virus. One of these carriers had an illness compatible with nonparalytic poliomyelitis. In summary, 1 paralytic case was followed by 3 other paralytic infections, 1 nonparalytic infection and 5 carrier states among 14 healthy contacts tested. Casey and his co-workers[7] have carried out extensive studies, also pointing out the importance of contact.

From these studies one can conclude that poliomyelitis virus has a world-wide distribution; that clinically recognized epidemics of poliomyelitis infections are of relatively recent origin and have been particularly prominent in the countries with high sanitation (this may mean that in countries of poorer sanitation, infections are occurring in the younger age groups with resulting immunity, but not associated with the usual signs of poliomyelitis); that close personal contact between apparently healthy carriers or clinical cases and susceptible hosts plays an important role in this widespread dissemination of the virus; and that

something happens during the summer in the temperate zones to increase this dissemination of virus (this may be explained by insect transmission, but other possibilities such as changes in the host or the virus itself may prove to be more important).

Prevention

The epidemiology of poliomyelitis is important, for it leads to a discussion of prevention. The first approach is to try to prevent the dissemination of the virus. Although the most important pathway of infection is not known, the foregoing discussion suggests certain steps to minimize the transfer of the virus. Ordinary contact in schools, movies and churches may play some role, but intimate contact between children during epidemics appears to be the most dangerous factor in the spread of the virus, and should be reduced to a minimum. Foods commonly eaten raw should be washed, and all milk should be pasteurized. In addition, the possibilities of transfer of virus by flies should be minimized by fly-abatement programs and screening of all food in stores, restaurants and kitchens. Screening flies away from exposed feces in privies and toilets should be done, and further studies should be encouraged on ways to inactivate the virus present in sewage.

The second approach is to try to reduce the number of paralyzing infections among susceptible persons who have become carriers of the virus. There is evidence that exhaustion, severe chilling, coincident gastrointestinal infections and operations on the nose and throat may make the difference between a carrier state, or nonparalytic infection, and a case of paralysis. For this reason these conditions should be avoided during epidemic periods.

The third approach is to produce artificial immunity to poliomyelitis. Because of ignorance of the exact mode of transmission of the virus and because of the practical difficulties of applying what is known about it, the immunization of children against poliomyelitis is the greatest need in this field. Attempts in the past have met with failure either because the vaccines used did not produce immunity or because they were too dangerous by reason of containing live virus. New approaches to this problem are being made, and a satisfactory vaccine may be developed. If it can be proved that the people of the more unsanitary countries actually acquire immunity without demonstrable infection from exposure to the virus in early infancy, this may lead to an immunization procedure by the oral administration of virus. This idea has appealed to many people, but obviously it cannot be undertaken lightly.

Treatment

The treatment of poliomyelitis is still hampered by the lack of a specific viricidal agent. The temporary popularity of serum from convalescent patients has waned, and few people believe that it has any beneficial effect. In the present state of ignorance the treatment resolves itself around nonspecific measures aimed at the relief of complications during the acute stage, making the patient comfortable, limiting spasm and contracture of the muscles, muscle re-education and the correction of resulting deformities.

Almost all the deaths from poliomyelitis are due to bulbar or respiratory involvement so that improved treatment for this form of the disease is particularly important. Some of these deaths have resulted from complicating pneumonia, which may be prevented or treated by the judicious use of chemotherapy or antibiotic therapy (sulfonamides, penicillin). The early recognition and treatment of atelectasis may prevent some of the deaths. A more recent development is the early use of tracheotomy and oxygen therapy in selected cases described by a team of workers at the University of Minnesota,[8] who have shown that many patients with bulbar involvement have difficulty getting a good respiratory exchange even in the respirator. By the use of tracheotomy, alone or in conjunction with the respirator, and by the liberal use of oxygen they believe that they have pulled many patients through who would otherwise have died. Their criteria for tracheotomy were: "Respiratory distress as evidenced by recurrent cyanosis, coarse rales in the chest and laryngeal stridor; excitement and unmanageability causing the patient to resist pharyngeal aspiration; stupor of a degree sufficient to make the patient oblivious of the accumulation of secretion in his airway; inability to cough effectively; pharyngeal pooling of mucus, vocal cord paralysis (or intralaryngeal hypesthesia demonstrable by laryngoscopy)."[9]

Another annoying and occasionally serious complication is paralysis of the bladder. Recent experience has shown that most of these patients can be relieved by the use of one of the new parasympatheticomimetic drugs, furmethide (furfuryltrimethylammonium iodide).[10] This is given subcutaneously in doses of 1.5 to 5.0 mg. according to age, and is usually followed by voiding in five to ten minutes. The drug may have to be repeated, but spontaneous voiding is usually re-established after the first dose. In a short series of cases it has been found that catheterization, with its discomfort and attendant danger of urinary infection, can be avoided in the majority of cases.

The main treatment of poliomyelitis is symptomatic and at present is usually some modification of the Kenny technic. It is not necessary to dwell on Miss Kenny's theories regarding the therapy that she has gradually evolved, for these theories are not accepted as being tenable.

It has been pointed out that all her therapeutic measures of positioning in bed, hot applications and early muscle re-education have been described

before and used extensively in one clinic or another. It is not fair to Miss Kenny, however, to claim that nothing is new in her scheme of treatment, for it is quite apparent that these methods had given way in previous years to prolonged immobilization in splints or casts, followed by late muscle re-education. A few physicians never adopted the prolonged use of casts and splinting, but the majority had done so before Miss Kenny's appearance. Now very little of this type of immobilization is being practiced.

The chief differences in the Kenny regime and so-called "orthodox" treatment are that muscle re-education, including passive motion of the extremities, is started earlier in the Kenny program; that immobilization is much more complete in the "orthodox" method; and that Miss Kenny treats contractures by application of heat and tendon stretching rather than by corrective appliances.[11, 12]

There are many minor variations in the technic of treatment, of course, but it does not seem that many of them are important. Many different methods of treatment between these two extremes have been used for the past thirty years. Some men carried out a program of treatment very similar to Miss Kenny's for years before her advent. At the present time most medical centers have adopted treatment schemes that are very similar to the Kenny method, without its rigid barriers to modification.

It is of interest to compare, if possible, the results of treatment by these various methods. One cannot be dogmatic about such a comparison, for each investigator has a different method of evaluating results. However, a review of all the available articles that include specific figures shows very similar therapeutic results. Mortality rates over the past thirty years have varied, and there has been some variation in end results, but there appears to be no really significant difference in results obtained by the various methods.[13]

The first fairly satisfactory statistics from the Kenny Institute fail to prove any superiority for this method of therapy. I for one, however, would not go back to the period of long immobilization in casts. It is impossible to agree with Miss Kenny's pseudoscientific reasoning, but it does seem that her method of treatment is more comfortable for the patient and probably makes the recovery of muscle function easier, since the peripheral tissues are kept in better tone.

The only other new developments in therapy during the past few years have been the use of prostigmine and curare for the relief of muscle spasm. In the absence of proved value the latter is too dangerous for use at the present time, although it does warrant further study. The value of prostigmine also is not well proved. Because of the variability of this disease, many better controlled studies will have to be made before one can assess the worth of either of these drugs. Fortunately, most children with poliomyelitis will escape paralysis regardless of the method of treatment employed, and even those who are paralyzed will improve their muscular co-ordination and efficiency if treated over long periods by experienced personnel.

Conclusion

In conclusion it may be noted that the picture is confused, but it is getting clearer. Newer theories regarding epidemiology, prevention and therapy have the support of well controlled clinical observation and experimentation. The outlook is better already, and investigators may well be on the brink of new discoveries that will allow conquest of this disease.

References

1. Paul, J. R. Poliomyelitis in Japan. *Am. J. Hyg.* **45**:206-218, 1947.
2. Paul, J. R., Havens, W. P., Jr., and Van Rooyen, C. E. Poliomyelitis in British and American troops in Middle East: isolation of virus from human faeces. *Brit. M. J.* **1**:841-843, 1944.
3. Howe, H. A., Bodian, D., and Wenner, H. A. Further observations on presence of poliomyelitis virus in human oro-pharynx. *Bull. Johns Hopkins Hosp.* **76**:19-24, 1945.
4. Brown, G. C., Francis, T., Jr., and Pearson, H. E. Rapid development of carrier state and detection of poliomyelitis virus in stool nineteen days before onset of paralytic disease. *J. A. M. A.* **129**: 121-123, 1945.
5. Horstmann, D. M., Ward, R., and Melnick, J. L. Persistence of virus excretion in stools of poliomyelitis patients. *J. A. M. A.* **126**:1061, 1944.
6. Gear, J. H. S., and Mundel, B. Studies in poliomyelitis: study of outbreak of poliomyelitis occurring in suburb of Johannesburg. *South African M. J.* **20**:106-140, 1946.
7. Casey, A. E., Fishbein, W. I., and Bundesen, H. N. Transmission of poliomyelitis by patient to patient contact. *J. A. M. A.* **129**:1141-1145, 1945.
8. Minnesota Poliomyelitis Research Commission. Bulbar form of poliomyelitis. II. Therapeutic measures based on pathologic and physiologic findings. *J. A. M. A.* **135**:425-428, 1947.
9. Priest, R. E., Boies, L. R., and Goltz, N. F. Tracheotomy in bulbar poliomyelitis. *Ann. Otol., Rhin. & Laryng.* **56**:250-263, 1947.
10. Lawson, R. B. Use of furmethide (furfuryltrimethylammonium iodide) for paralysis of bladder from poliomyelitis. *South. M. J.* **41**:251-255, 1948.
11. Key, J. A. Reasons why orthodox is better than Kenny treatment of poliomyelitis. *Surg., Gynec. & Obst.* **77**:389-396, 1943.
12. Pohl, J. F. Kenny concept and treatment of infantile paralysis: report of five year study of cases supervised by Miss Elizabeth Kenny in America. *Journal-Lancet* **65**:265-271, 1945.
13. Lawson, R. B. Treatment of acute anterior poliomyelitis. *North Carolina M. J.* **8**:26-29, 1947.

Additional Reference

Ward, R. Poliomyelitis: review of its natural history. *Physiotherapy Rev.* **27**:213-218, 1947.

LIPEMIA IN HEMOCHROMATOSIS*

Report of a Case

ALFRED R. LENZNER, M.D.,† AND BYRON D. BOWEN, M.D.‡

BUFFALO, NEW YORK

THE occurrence of lipemia in hemochromatosis has not been described in the literature, to our knowledge. The recognition, therefore, of an opaque serum taken from an otherwise typical patient in the fasting state was quite surprising. But so are several variants of hemochromatosis reported since Trousseau's first casual allusion to this syndrome in 1865.[1] For example, of the

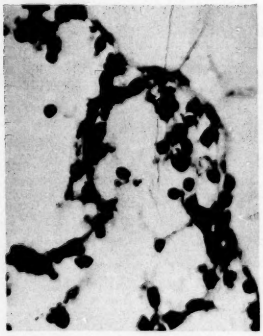


FIGURE 1. *Section of Bone Marrow Aspirated from the Iliac Crest, Showing Increased Amounts of Hemosiderin in Reticular and Sinus Epithelial Cells (High-Power, Hemosiderin and Eosin Stain).*

triad of cirrhosis of the liver, diabetes mellitus and pigmentation, cirrhosis only seems to be constant. In some cases diabetes has been proved not to have been present.[2, 3] Others[4] have been unable to demonstrate intradermal pigment, despite apparently typical pigmentation. Moreover, the pathological physiology itself is obscure. One salient fact stands forth, however: these patients do retain abnormal amounts of iron salts.[5] Sheldon[1] has estimated that the total iron content in hemochromatosis may lie between 25 and 50 gm., as compared with a normal of approximately 3 gm.

Up to the present, figures seem to matter little. Those for the increased serum fat in this case are readily available. So far as they might indicate etiology per se, they are of as much aid as those for the total iron content would be. The present circumstance, however, does give occasion for careful reconsideration of the causes of postabsorptive lipemia.

CASE REPORT

A 56-year-old fireboat deckhand was admitted to the hospital in July, 1947, with the chief complaint of failure to gain weight. Diabetes mellitus had been diagnosed 18 months previously, after he had noted polyuria for 8 weeks. These symptoms were accompanied by a 30-pound weight loss. His physician had placed him upon 35 units of protamine insulin daily. No change in weight had followed this regimen. Four months before admission, he had entered another hospital because of painful feet and nocturia. Hepatomegaly, diabetes and pigmentation had been noted by a medical student acting as a subintern. Roentgenograms of the legs had revealed a moderate amount of arterial calcification and mild osteoporosis of the bones of the feet. The first fasting blood glucose had been 211 mg. per 100 cc., a cephalin flocculation test had been ++, and the fasting serum collected

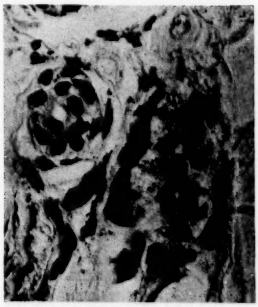


FIGURE 2. *Sweat Gland from the Dorsum of the Hand, Showing Hemosiderin Granules within the Basement Membrane (High-Power, Ferrocyanide Technic).*

for an icteric index was reported as "too cloudy" for determination. He had remained on 35 units of protamine insulin until he was admitted for evaluation of the diabetes and other studies.

The patient related that while in high school he had been nicknamed "Gypsy"; that he had frequently used argyrol swabs for "colds"; but that his skin had become distinctly darker during the onset of overt diabetes. Since the insulin had been started he had regained much of his former strength, there was no nocturia, and his feet had improved. He had had loss of libido and potency for 18 months. He denied alcoholism. The family history was suggestive of hemochromatosis in that his mother had also been dark skinned, but she had died at 75 years of age. His brother, killed acci-

*From the Buffalo General Hospital and the University of Buffalo School of Medicine.

†Assistant in medicine, University of Buffalo School of Medicine.

‡Professor of clinical medicine, University of Buffalo School of Medicine.

dentally at the age of 44, was the darkest of the family, but so far as is known he was not diabetic.

Physical examination revealed a bronze-gray cast of the exposed areas, the unexposed portions showing merely a peculiar dirty-blue pallor. The scleras were white. The mucosas were normal. The retinas were not remarkable. Occasional extrasystoles were noted, but the heart tones were of good quality. The liver was firm, smooth and nontender. It was enlarged four fingerbreadths and presented a rounded edge. The tip of the spleen was palpable. Angiomas and xanthomas were not present. The axillary and pubic hair were normal, but the genitalia showed mild atrophy. The rectal sphincter tone was good, and the prostate normal. Pedal pulses were present.

The blood pressure was 120/80.

The laboratory procedures are best enumerated as functional groups:

Hepatobiliary system. The albumin-globulin figures were 3.8:3.2. gm. The alkaline phosphatase was 10.2 Bodansky units. The cephalin flocculation was +++, and the thymol turbidity, 0 units. The prothrombin time was normal. The bromsulfalein test, 5 mg. per kg. of body weight per 45 minutes, showed about 10 per cent retention of the dye (serum, opaque); the total cholesterol was 208 mg., and the cholesterol esters, 68 mg. per 100 cc. The total serum lipids were 1057 mg. per 100 cc., and the lipochrome index, 2.6 units. A Graham–Cole test showed nonvisualization of the gallbladder after the administration of nine "priodax" tablets. Duodenal drainage then revealed normal "A" bile, but "B" bile could not be obtained.

FIGURE 3. *Liver Needle Section, Showing Hemochromatotic Cirrhosis (Low-Power, Hemosiderin and Eosin Stain).*

Pancreas. Pancreatic lipase and amylase were present in normal amounts in the duodenal contents; the stool fat and fatty acid content was not abnormal (Sudan III). Fatty acid crystals were not seen, nor were undigested fibers observed.

Kidneys. Urinalysis showed a trace of protein, but no formed elements. The urine concentration reached 1.015 after 15 hours' abstinence from fluids. The phenolsulfonephthalein excretion after adequate fluids was 40 per cent in 15 minutes, and totaled 50 per cent at the end of 2 hours. The serum phosphorus was 3.6 mg., and the blood urea nitrogen, 14 mg. per 100 cc.

Adrenal glands. The serum sodium was 318 mg., and the serum potassium, 11.4 mg. per 100 cc. A Kepler–Power water test[8] showed a night volume of 280 cc., the largest hourly day specimen measuring 90 cc. The quotient, however, was 30 according to Procedure II and, therefore, negative.

FIGURE 4. *Portion of the Liver Needle Section, Showing Hemosiderin Granules within the Liver Cells, the Bile-Duct Epithelium and the Fibrous Stroma (High-Power, Ferrocyanide Technic).*

Hematopoietic system. The hematocrit was 40 per cent. The red-cell count was 3,800,000, and the hemoglobin 11.2 gm. (photometric technic). No macrocytosis was evident. The gastric contents were acid after histamine. Bone-marrow smears obtained from the iliac crest showed a marked increase in erythropoiesis, mild myeloid maturation arrest and hemosiderosis of fixed cells. Pathological sections of the clotted marrow showed that it was moderately fatty. Increased amounts of hemosiderin were present within the reticular and the sinus epithelial cells (Fig. 1).

A skin biopsy obtained from the dorsum of the hand revealed slight to moderate amounts of hemosiderin about the sweat glands (Fig. 2).

Liver needle biopsy showed a well established portal cirrhosis with moderate bile-duct proliferation. Abundant pigment was present within the fibrous stroma, and smaller amounts were found within the hepatic cells proper, as well as within the bile duct epithelium (Fig. 3 and 4). No active degenerative changes were evident.

The hemosiderin present in all three locations exhibited the ferrocyanide reaction characteristic for this pigment.

DISCUSSION

The clinical picture in this case was sufficiently characteristic to make its discussion unnecessary. The lipemia, however, warrants some consideration. Since it most probably reflects primary digestive-organ impairment, the interrelated functions of the liver, the pancreas and the gastrointestinal tract are involved to a variable degree. Of course, lipemia is a feature of the nephrotic syndrome, but this need not be considered here.

The gastrointestinal tract is probably not at fault. This is a postabsorptive lipemia. As such, it is somewhat more logical to assume that this mani-

festation reflects an inadequacy of assimilation rather than excessive absorption. Before assaying the contributory roles of the liver and the pancreas, however, an examination of the physical and chemical characteristics of this lipemia may be helpful.

The term "lipemia" as it is used here is a clinical one — that is, it refers to visible amounts of fat in the fasting serum or plasma. The opacity is due to fats in their neutral phase. According to Thannhauser,[7] this is usually but not necessarily always accompanied by hypercholesteremia. Conversely, markedly elevated serum cholesterol and phospholipid levels are exhibited in the perfectly transparent serums of patients with primary biliary "xanthomatous" and cholangiolitic types of cirrhosis. These patients do not have lipemia, however, for their neutral fats are normal in amount. In this case excess neutral fats were not accompanied by an increase in either phospholipids or cholesterol (Table 1).

This fat pattern is a key consideration. It immediately eliminates idiopathic hyperlipemia,

TABLE 1. *Serum Fat Analysis.**

	PATIENT	NORMAL CONTROL
	mg. per 100 cc.	*mg. per 100 cc.*
Total fatty acids	599	200–400
Neutral fat	370	0–150
Total phospholipids	151	150–250
Total cholesterol	219	150–260
Cholesterol esters	139 (64%)	70% of total

*Reported through the courtesy of Dr. Siegfried J. Thannhauser, of Boston.

which is characterized by elevated cholesterol and phospholipid levels, in addition to the high neutral fats shown here.

The liver, moreover, is apparently not the prime mover in this lipemia. For although previous laboratory data had shown hepatic dysfunction, the essentially normal phospholipid, cholesterol and cholesterol-ester relations indicated that the hepatic phase of fat metabolism was unremarkable. Man et al.[8] concluded from similar fat studies that a "hypolipemia" usually exists in cirrhosis. The neutral fat seldom exceeded the upper limit of normal, the cholesterol and lipid phosphorus were either normal or decreased, and the cholesterol esters were often decreased. Aside from the pigment present in this liver, the process here is identical with that in Man's cases, and should not per se produce a hyperlipemia of this type. Although some of Thannhauser's cases exhibited mild elevations of neutral fat, these apparently occurred with depressed hepatic function, as shown by manifestly poor cholesterol esterization. Such a depression of function was not observed in the case reported above.

The pancreas, however, may be responsible for this lipemia, by virtue of either islet-cell or even acinar-cell dysfunction. Primary diabetes under control should not logically produce a persistent postabsorptive neutral hyperlipemia. Man and Peters[9] concluded that "abnormalities of the serum lipoids are related loosely, if at all, to diabetes." When lipemia and hypercholesteremia did occur, these could not be correlated with the "inherent severity of the (islet cell) disease as measured by any recognized criteria." Alloxan diabetes in rabbits[10] and in dogs,[11] moreover, when controlled by insulin, failed to produce a hyperlipemia (total serum lipids). But high lipids and cholesterol accompanied fatal alloxan diabetes in all of Kendall's[12] animals.

The patient in the case reported above is a "fragile" diabetic. On 50 units of protamine zinc insulin daily his blood glucose levels have always been low (less than 100 mg. per 100 cc.), with rather high postprandial values (more than 240 mg. per 100 cc.) and glycosuria. There has been no ketosis, however, and the transiently elevated glucose levels should not furnish cause for this lipemia. He has never exhibited clinical shock. Islet-cell diabetes, therefore, does not strike one as being the causative agent here.

Finally, the acinar tissue of the pancreas should be mentioned. The presence of adequate duodenal pancreatic ferments, together with normal stool findings, seems to absolve the acini. Perhaps these tests are too gross for this type of disease. Nevertheless, even the technic of Bauman and Whipple[13] proved more helpful in obstructive pancreatic disease than in the sclerosing type characteristic of hemochromatosis. The evidence against the pancreatic acini is only circumstantial, to be sure, and yet one has the feeling that the pancreas is more guilty than the liver in this case.

Most studies of the pancreas in fat metabolism mention fat accumulations in the liver. It should be pointed out that the remaining liver parenchyma and its regenerates here are not fatty. This is true despite the lipemia and probably pancreatic insufficiency — a combination that might be considered ideal for the production of fatty liver. Here, as also in "idiopathic hyperlipemia," the liver is kept free from fat accumulations in an "environment of plenty," so to speak. One cannot, therefore, identify the specific reason for this lipemia with certainty.

At present, more than two years since his diabetes was first discovered, and despite a gradually increasing lipemia, the patient works every day. The fasting urine remains sugar free on 50 units of protamine zinc insulin. But the underlying lesion apparently continues unabated, for a dermal scar at the site of the liver biopsy has developed the gunmetal pigmentation often associated with hemochromatosis.

SUMMARY

A case of lipemia associated with hemochromatosis is reported. Skin biopsy, liver needle sections

and bone-marrow aspirations showed hemosiderin deposits. Probable factors in this lipemia are suggested, though none can be proved.

References

1. Trousseau. Cited by Sheldon, J. H. *Haemochromatosis*. 382 pp. London: Oxford University Press, 1935.
2. Butt, H. R., and Wilder, R. M. Hemochromatosis: report of thirty cases in which diagnosis was made during life. *Arch. Path.* **26**:262-273, 1938.
3. Humphrey, A. A., Alpiner, S., and Verity, L. E. Hemochromatosis: report of case and comment on methods of making definite diagnosis. *Arch. Dermat. & Syph.* **45**:1128-1132, 1942.
4. Cantarow, A., and Bucher, C. J. Hemochromatosis: report of case. *Arch. Int. Med.* **67**:333-344, 1941.
5. Marble, A., and Smith, R. M. Studies of iron metabolism in case of hemochromatosis. *Ann. Int. Med.* **12**:1592-1603, 1939.
6. Levy, M. S., Power, M. H., and Kepler, E. J. Specificity of "water test" as diagnostic procedure in Addison's disease. *J. Clin. Endocrinol.* **6**:607-632, 1946.
7. Thannhauser, S. J. Serum lipids and their value in diagnosis. *New Eng. J. Med.* **237**:515-521, 1947.
8. Man, E. B., Kartin, B. L., Durlacher, S. H., and Peters, J. P. Lipids of serum and liver in patients with hepatic diseases. *J. Clin. Investigation* **24**:623-643, 1945.
9. Man, E. B., and Peters, J. P. Serum lipoids in diabetes. *J. Clin. Investigation* **14**:579-594, 1935.
10. Bailey, C. C., Bailey, O. T., and Leech, R. S. Alloxan diabetes with diabetic complications. *New Eng. J. Med.* **230**:533-536, 1944.
11. Goldner, M. G., and Gomori, G. Alloxan diabetes in dog. *Endocrinology* **33**:297-308, 1943.
12. Kendall, F. E., Meyer, W., Lewis, L., and Victor, J. Alloxan diabetes in rabbits. Production of hypercholesterolemia, hyperlipemia and adrenal cortical lesions. *Proc. Soc. Exper. Biol. & Med.* **60**:190-195, 1945.
13. Bauman, L., and Whipple, A. O. Diagnostic value of pancreatic function tests in 47 surgically treated cases. *Am. J. M. Sc.* **281**:290, 1944.

THE MEDICAL EXAMINER AND THE PRACTICING PHYSICIAN*

Richard Ford, M.D.†

BOSTON

In the Commonwealth of Massachusetts, medical examiners and associate medical examiners are county officers appointed for a term of seven years for the purpose of investigating certain classes of deaths. Chapter 38 of the *General Laws* of the Commonwealth (as amended by Chapter 632 of *Acts and Resolves* of 1945) states:

> When any person in the Commonwealth is supposed to have died by violence or by the action of chemical, thermal or electrical agents or following abortion, or from diseases resulting from injury or infection relating to occupation, or suddenly when not disabled by recognizable disease, or when any person is found dead, it shall be the duty of any person having knowledge of such death to notify the medical examiner of the district of the county wherein the body lies of the known facts concerning the time, place, manner, circumstances, and cause of such death. A physician who, having knowledge of such a death, fails to notify the medical examiner shall be punished by a fine of not more than one hundred dollars.

In brief, the six categories of deaths to be investigated are violent; chemical, thermal or electrical; deaths resulting from induced abortion; occupational deaths resulting from injury or infection; sudden deaths in the absence of recognizable disease; and persons found dead.

On receipt of notification of a death, there are three courses open to the medical examiner. He may decline jurisdiction over the case, referring it to the attending physician or to a board-of-health physician (if there is one) for certification regarding the cause of death. He may assume jurisdiction, scrutinize available information, make a *view* of the body (external examination) and certify the cause of death himself. Or he may view the body and then perform an autopsy or cause one to be performed.

When may a medical examiner decline jurisdiction? He may decline when, after ascertaining the available facts, he is satisfied that the death was caused by disease not related to the six categories outlined above.

Who shall certify a death when the medical examiner declines? The attending physician shall certify if he is available and if he attended the decedent at least twice, the last visit being within two weeks before death. If the physician who attended the decedent during his terminal illness is not available or if there has been no attending physician, a board-of-health physician may certify. Thus, board-of-health physicians (in areas where they are appointed) certify the deaths of those disabled by recognized disease not related to the six categories of medical-examiner cases when the attending physician has not seen the decedent within two weeks or when he is absent. Either the mother's physician or a board-of-health physician may certify stillbirths if there has been obstetric or general medical care prior to the birth, and if there is no question of violence, illegitimacy or birth injury.

What are the rules requiring that cases be reported to the medical examiner? The rules of practice vary somewhat among the medical-examiner districts and are evolved usually by collaboration between the medical examiner and the local board of health. In most districts the following cases should be reported:

Any death thought to fall into one of the six categories established by the *General Laws*.

Any hospital death within twenty-four hours of admission.

Any hospital death when the decedent was unconscious on admission and remained so.

*From the Department of Legal Medicine, Harvard University and the Office of the Associate Medical Examiners, Suffolk County, Massachusetts.

†Research fellow in pathology and legal medicine, Harvard Medical School; associate medical examiner, Suffolk County.

Any death pronounced by a physician other than the attending physician.

Any death when the patient was not attended by a physician within two weeks.

All such cases should be reported, but many will be declined at the time of reporting, and others after a preliminary investigation. For example, a man who collapsed at home or in his office and died fifteen minutes after hospital admission may be found to have been treated by the referring physician for a myocardial infarction five days previously. In another case in which a woman dies within twenty-four hours of admission to a hospital in coma the medical examiner may infer from the excessive obesity of the patient, from a positive history of hypertension and from a negative history of trauma that death was due to natural causes. Such cases may be declined by the medical examiner if he is satisfied that there are no reasonable grounds for suspecting that the death was caused or contributed to by physical or chemical injury or occupation.

What is the limit of time between injury and death within which a death must be reported to the medical examiner? There are no limits if the reporting physician believes that the injury caused or contributed to the death. Although the passage of time between injury and death may eliminate criminal responsibility, prevent tort action (damage suit) and make insurance claims contestable, intricacies of law, as when the damage was recognized, make it imperative that the medical examiner make an official record of the circumstances. Where there is not a clearly demonstrable relation between injury and death, the medical examiner may apply the British rule and decline such cases having a time interval in excess of a year and a day.

When may a medical examiner perform an autopsy? According to Chapter 38 of the *General Laws*, as amended:

> If on view of the dead body and after personal inquiry into the cause and manner of death, the medical examiner considers a further examination necessary in the public interest . . . [he] on his own authority may . . . make or cause to be made in his presence, an autopsy on the aforesaid body.

In other words, medical examiners are required to perform an autopsy only if it appears to be necessary in the public interest. A death that is a police matter is apt to require post-mortem examination, either to exonerate a suspect or to substantiate a suspicion. In general, cases likely to reach the criminal courts require autopsy. A death thought to be the result of virulent contagious disease may well require post-mortem confirmation because of the possible hazard to public health. A death related to occupation in industry, as a result of either injury or infection, may require autopsy in the public interest if others in that industry are exposed to the same hazard. Post-mortem examination of the body of an unknown person found dead may be desirable first, to determine the cause of death and, second, to provide information about the presence of chronic disease, the nature of past surgical procedures, old injuries, and any other anatomic fact that might add to the description of the unknown.

When the circumstances have established that an autopsy may reasonably be required in the public interest, the second criterion should be met — namely, that post-mortem dissection is *necessary* to establish either cause or manner of death. The body of a man who was seen by reliable witnesses to slip, fall and strike his head and who subsequently died in a hospital with x-ray films showing extensive fractures of the skull does not ordinarily require autopsy. If, on the other hand, a man were found unconscious on the street and subsequently died in a hospital without regaining consciousness and with signs of severe head trauma it would be necessary to perform a postmortem examination to determine to the fullest extent the nature of the injuries. Thus, it is in the public interest to establish whether there was one or multiple impacts; the size and the shape of the object that produced injury; and the presence or absence of disease or intoxication that may have predisposed the deceased to accident or assault. In essence, then, an official autopsy is necessary in cases in which precise detail regarding cause is of value, such as those destined for criminal courts, those in which the manner of death may be ascertained in part or in entirety by determination of the nature of injuries and those in which information contributing to identification may be acquired.

Under certain circumstances a medical examiner is required to perform an autopsy when so instructed:

> [The medical examiner] if he be so requested by the district attorney or the attorney general, shall make or cause to be made in his presence, an autopsy on the aforesaid body. . . . Upon written order of the district attorney of the district where the body lies, or of the attorney general, a medical examiner shall also make, or cause to be made in his presence, an autopsy. . . . of any dead body within this county.

In simpler wording, on request — verbal or written — of either the attorney general or the district attorney, a medical examiner is required to perform an autopsy.

It should now be clear that a medical examiner does not act according to whim. He declines jurisdiction, or accepts and views a case, or performs an autopsy according to certain rules, which are derived from the *General Laws* of the Commonwealth. The most important function of the medical examiner is to protect the public by the acquisition of accurate medical evidence in deaths known or suspected to have resulted from criminal action.

An almost equally important function is to assist in the protection of public health from epidemic disease and industrial hazards. An incidental function is to investigate and furnish official records of deaths resulting from trauma of any sort, thereby protecting the rights of employee and employer, policyholder and insurer, civil claimant and defendant in all claims and suits for damages.

In metropolitan areas friction sometimes exists between the resident staffs of the hospitals and the medical examiner's office. It is apparently the firm belief of many of the younger physicians that the medical examiner acts in an ignorant, capricious and indifferent manner, especially with respect to performing autopsies. It is hoped that the exposition of the duties and limitations of power of the office presented above may eliminate this impression. Such critics, if they grant that the medical examiner must certify the cause and manner of death of certain cases without the right to autopsy, complain that bodies are removed from the hospitals by the medical examiner merely for viewing at a mortuary or undertaking establishment without allowing medical attendants the opportunity to seek permission for post-mortem examination by the hospital pathologist. The major cause for removal of bodies solely for view is the inadequacy of information furnished by the hospital to the medical examiner. Frequently, when the reporting hospital is unavoidably limited in information the medical examiner's office must seek out police reports or the records of other hospitals, or perhaps initiate a police investigation. In the interim, after enduring delays due to locating witnesses and reaching hospital record rooms (open from 9 in the morning to 5 in the afternoon except Saturday afternoon and Sunday), the family has selected an undertaker, and the medical examiner has no right to delay the funeral further to enable the attending physicians to have additional time to solicit permission for autopsy. Sometimes the co-ordination between the administrative and professional staffs of a given hospital is at fault. A case may be declined by the medical examiner and the administration of the hospital notified, but no word is sent to the professional staff that the way is open to request permission.

Often there are limits to the physical capacity of the medical examiner to fulfill his prescribed duties. If during a twenty-four-hour period 10 medicolegal deaths are reported, with between 1 and 5 autopsies necessary in the public interest, it is obviously impossible to travel from place to place to view bodies under trying circumstances. There is, however, a solution to the difficulty. If each hospital were to designate a single physician with the experience and authority necessary to ensure complete and accurate reporting of medicolegal deaths and to facilitate the prompt viewing of bodies at the hospital, more cases would be available for hospital autopsy. No medical examiner, pathologist or general practitioner will deny that autopsy is desirable for the common good.

MEDICAL PROGRESS

BAL*

RAYMOND V. RANDALL, M.D., AND ALBERT O. SEELER, M.D.†

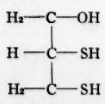
BOSTON

THE discovery of BAL (2,3–dimercaptopropanol) by Peters and his co-workers[1] in England was the result of an intensive search for a substance that would be effective in treating severe burns caused by contact with certain arsenical war gases such as lewisite. The name BAL is an abbreviation of "British Anti-Lewisite," a term applied to this substance after it had proved to be effective against lewisite. It was soon found that this compound was of value not only in treating the local effects of arsenical war gases but also in combating the systemic disturbances following their absorption. Moreover, BAL proved to be effective in the treatment of toxic reaction caused by arsenical drugs used in the therapy of syphilis. Further investigation showed that the substance was of value in the treatment of poisonings from a number of other metals.

The studies on BAL and related compounds have not only led to the development of a valuable therapeutic agent but also contributed to an understanding of the mode of action of various metals.

CHEMISTRY AND PROPERTIES[2–4]

The chemical name for BAL is 2,3–dimercaptopropanol. It contains two thiol groups (also known as sulfhydryl [–SH] groups) and consequently 2,3–dithiopropanol is a commonly used synonym. Its structural formula is:



BAL has a molecular weight of 124.2 and a specific gravity of 1.21, and is an oily, colorless liquid with a skunklike odor. In common with a number of closely related dithiols, the compound is a sluggish, nonautoxidizable, oxidation-reduction system, easily oxidized in the presence of a number of catalysts, especially copper and iron porphyrins. BAL reacts with a number of metals to form BAL–metal complexes. Colored complexes are formed with iron, lead, bismuth, tin, copper, cobalt, nickel, antimony and selenium. Zinc, cadmium and mercury combine with BAL to give white precipitates, and magnesium and manganese form colorless, soluble complexes. BAL instantaneously converts methemoglobin to oxyhemoglobin in the presence of oxygen.

BAL is soluble in water to the extent of 6 per cent (weight/volume). Because it is readily oxidized, aqueous solutions are unstable and must be prepared immediately before use. The compound is relatively stable in peanut oil, but soluble in this vehicle only to the extent of 5 per cent (weight/volume). However, when it is mixed with benzyl benzoate in the ratio of 1 part of BAL to 2 parts of benzyl benzoate it is miscible with peanut oil in all proportions. Such preparations are homogenous but become cloudy at icebox temperatures. This cloudiness readily disappears when the preparation is warmed to room temperature. Commercial preparations of BAL contain 10 per cent BAL and 20 per cent benzyl benzoate (weight/volume) in peanut oil and are suitable for intramuscular use only. Sterilization of such preparations by autoclaving at 120°C. for twenty minutes may cause the loss of as much as 15 per cent of the available sulfhydryl groups by oxidation. If, however, these preparations are placed under nitrogen they may be autoclaved without significant decomposition.

MODE OF ACTION OF HEAVY METALS AND BAL

During the past twenty-five years, the concept has arisen that heavy metals owe their toxicity, at least in large part, to their ability to combine with sulfhydryl groups of the protein fractions of enzymes. Studies that ultimately led to this concept and to the development of BAL began in 1923 when Voegtlin, Dyer and Leonard[5] showed that glutathione, as well as other monothiols (substances containing one thiol or sulfhydryl group), could counteract the toxic action of arsenoxides on trypanosomes both in vitro and in vivo. They further showed that glutathione delayed the onset of symptoms and death in rats given a lethal dose of arsenoxide. On the basis of these findings, they postulated that arsenoxide could be regarded as a specific poison affecting the sulfhydryl groups of some essential protoplasmic constituent. The addition of the monothiols presumably supplied extra sulfhydryl groups, which united with and thereby counteracted the toxicity of the arsenic. The au-

*From the Department of Industrial Hygiene, Harvard School of Public Health.

This study was aided by a grant from the Medical Advisory Committee of the American Petroleum Institute.

†Assistant professor of industrial medicine, Harvard School of Public Health.

thors also assumed that the union between the arsenic and the added sulfhydryl groups was not stable — otherwise glutathione would have prevented rather than merely delayed death in rats given lethal doses of arsenic. Further evidence of the relation of sulfhydryl groups to the toxicity of arsenic was the observation of Walker[6] in 1928 that *Colpidium colpoda*, a unicellular organism, could be temporarily revived after arsenic poisoning by the addition of sodium thioglycollate.

Similarity in the mode of action of arsenic, bismuth and mercury compounds was demonstrated in 1939 by Eagle,[7] who showed that various sulfhydryl-containing substances abolished the antispirochetal action in vitro of bismuth and mercury as well as of arsenic. He found that thiamine chloride and methionine, which contain sulfide (–S–) rather than sulfhydryl (–SH) groups did not have a similar inhibitory effect on these heavy metals

Studies on proteins and enzyme systems have also been carried out in an attempt to discover the mode of action of arsenic. Szent-Györgyi,[8] in 1930, showed that arsenic strongly inhibited the respiration of minced liver tissue. Voegtlin, Rosenthal and Johnson[9] found that glutathione added to rat tissue slices prevented the reduction in oxygen consumption caused by arsenic alone. These findings also suggested that sulfhydryl groups were intimately concerned with tissue respiration, and that the action of arsenic upon living tissue was primarily through the tissue's sulfhydryl compounds. Further evidence in support of these views was forthcoming in 1932, when Rosenthal[10] showed that although arsenic combined with proteins containing sulfhydryl groups, it did not combine with proteins in the absence of these groups.

In the course of studies on arsenical war gases, Peters, Sinclair and Thompson[11] found the enzyme pyruvate oxidase to be sensitive to small concentrations of arsenic or lewisite. Since none of the coenzymes known to be concerned with the pyruvate oxidase system were sensitive to lewisite, it was concluded that the point of attack of arsenic was upon a protein component of the enzyme system. It was soon demonstrated that a protein containing sulfhydryl groups was essential for the function of pyruvate oxidase and that blockage of these groups would inactivate the enzyme.[12] These findings indicated that the toxic action of arsenic was due, not to some nonspecific denaturant or coagulant effect upon cellular constituents, but to enzyme inhibition.

In contrast to the work mentioned above, wherein it had been found that monothiols afforded protection against various arsenic compounds, Sinclair (as quoted by Peters et al.[1]) found that monothiols, even when present in large excess, failed to protect pyruvate oxidase from the toxic action of lewisite. It, therefore, seemed important to reinvestigate the nature of the union between arsenic and protein sulfhydryl groups. Since it was impossible to obtain an arsenic-sensitive enzyme, such as pyruvate oxidase, in a purified state, Stocken and Thompson[13] studied kerateine, a derived protein containing many sulfhydryl groups. They found that at least 75 per cent of the arsenic in the lewisite-protein complex was in combination with two sulfhydryl groups. Additional findings made it seem probable that the arsenic had combined with two sulfhydryl groups closely placed on the same protein molecule to form a ring. On physiochemical grounds it was predicted that

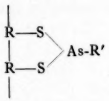


FIGURE 1. *Ring Structure.*

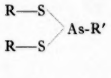


FIGURE 2. *Open-Chain Structure.*

a ring compound (Fig. 1) would be more stable than an open-chain structure formed by the union of arsenic with two monothiol molecules (Fig. 2). On the basis of this reasoning, it appeared that a substance capable of competing successfully with tissue proteins for arsenic must also be capable of forming a ring compound as stable as, and preferably more stable than, that formed between arsenic and the proteins. Supporting this view was the work cited above[5-7] showing that monothiols delayed but did

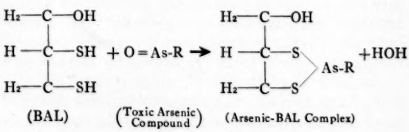


FIGURE 3. *Reaction Between Arsenic and BAL.*

not always prevent the death of animals poisoned with arsenic.

Stocken and Thompson[14] decided to experiment with various dithiols because they believed that these compounds with their two sulfhydryl groups might be capable of forming stable cyclic combinations with arsenic. Numerous dithiols were tested, some with as many as 12 carbon atoms between the two sulfhydryl groups, and a number were found to react with arsenic to form a stable ring structure. However, not all the latter compounds were satisfactory on pharmacologic grounds, and it was only after extensive animal studies that BAL was selected as the most promising compound.

It now seems clear that the antidotal action of BAL lies in its ability to unite with arsenic to form a relatively stable cyclic compound and thus to compete successfully with the sulfhydryl groups of tissue proteins for arsenic. This action is both prophylactic and therapeutic, because BAL can unite with arsenic before it enters into combination with the tissues (Fig. 3) as well as wrest arsenic away from the tissues (Fig. 4).

Pharmacology

Action on Enzymes

In an attempt to arrive at an understanding of the toxicity of BAL, Webb and van Heyningen[15] studied its action on a large number of enzyme systems. They found seven enzymes to be strongly inhibited by BAL: polyphenol oxidase, carbonic anhydrase, catalase, peroxidase, aldehyde mutase, phosphorylase and glyoxalase. Of these, four are known to be metal-containing enzymes: polyphenol oxidase (copper), carbonic anhydrase (zinc), catalase (iron), and peroxidase (iron). In view of the fact that BAL forms complexes with these metals[3] it is likely that it inhibits the enzymes by combining with their metal radicals. In further support of this hypothesis is the finding that the addition of a copper salt to polyphenol oxidase inhibited by BAL restores the activity of this copper-containing enzyme. Cytochrome oxidase is the only metal-containing enzyme that was examined and found not to be inhibited by BAL. This was thought to be due to a rapid oxidation and inactivation of BAL when it comes in contact with this enzyme. No explanation is offered for the inhibition of aldehyde mutase and phosphorylase, although it is pointed out that these, too, may be metallic enzymes. It is believed that glyoxylase, which does not contain a metal but does contain glutathione (a monothiol), is inhibited by BAL, because the BAL can compete successfully with the monothiol for a position in the enzyme structure.

Barron et al.[16] found that BAL decreased the respiration of tissue slices and inhibited cytochrome C and succinoxidase. They also noted that BAL destroyed the activity of insulin by reduction of its –S–S– linkages.

Absorption, Metabolism and Excretion[17-21]

Studies with radioactive BAL (BAL containing radioactive sulfur) have shown that it is slowly absorbed through the skin but rapidly dispersed once it penetrates the cutaneous barrier. Radioactive BAL given intramuscularly has disappeared rapidly from the site of injection, with no radioactivity remaining at the site after six hours. Within five minutes after instillation into the conjunctival sac of the rabbit, BAL has been recovered from the aqueous of the anterior chamber.

Experiments with rabbits given intramuscular injections of radioactive BAL have shown that 80 per cent of the injected BAL entered the circulation and was distributed throughout the body within an hour of injection. A fairly uniform blood level was maintained for two hours. This level was halved by the third hour, and fell to a third of the original value by the seventh hour. Aside from somewhat higher concentrations in the kidney and intestine, BAL was diffusely distributed throughout the body.

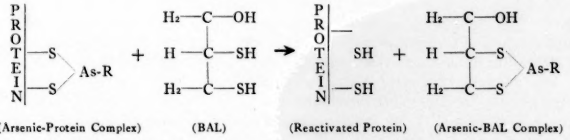


FIGURE 4. *BAL Reactivation of an Arsenic-Poisoned Tissue Protein.*

Only minute amounts of BAL have been found to be excreted by the respiratory tract although its skunklike odor may be detected in the expired air. Studies have shown that the major portion of absorbed BAL is rapidly metabolized and excreted in the urine. After single injections of radioactive BAL, 45 per cent of the total radioactivity could be recovered from the urine within six hours, and 81 per cent within twenty-four hours. Only a small proportion of the radioactive substances recoverable from the urine was in the form of unchanged BAL.

Action on Animals

In general, the signs and symptoms of BAL toxicity are ushered in by an initial period of apathy accompanied by lacrimation, blepharospasm and conjunctival edema. With increasing dosage, one finds in addition to the above: muscle tremors of gradually increasing intensity; inco-ordination; ataxia, especially of the hind limbs; dyspnea; and finally generalized clonic convulsions, coma and death. Only an occasional animal recovers once convulsions have begun. An early transient rise in

blood pressure is common, but this soon gives way to vascular collapse.[22, 23]

Undiluted BAL applied directly to the skin and mucous membranes causes localized redness, edema and capillary injury.[23, 24]

Electroencephalograms taken during BAL-induced convulsions in rabbits have revealed that they are not cortical in origin. Studies following transection of the thoracic cord further showed that the convulsions do not arise in the cord. The exact site of origin has not been established. Sodium pentobarbital controlled these convulsions, but death from vascular collapse usually occurred.[22]

In moderate doses, BAL is a respiratory stimulant. Large doses stimulate respiration initially, but severe depression of the respiratory center follows.[22, 23]

BAL causes an initial arteriolar constriction resulting in a rise in blood pressure. This effect is not mediated through the central nervous system, but is the result of a direct action upon the vessel walls. Subsequently, BAL may cause extensive capillary damage, which can lead to irreversible shock.[25, 26]

In dogs, an intramuscular, lethal dose of BAL (100 mg. per kilogram of body weight) has produced early hyperglycemia with glycosuria and subsequent preterminal hypoglycemia. Convulsions occurring in these animals were not hypoglycemic because they began while the blood sugar was still elevated. Histologic examination of the liver failed to reveal any evidence of hepatic-cell damage.[22] However, fatty degeneration and occasional necrosis have been found in the livers of dogs given daily intramuscular doses of 15 to 30 mg. per kilogram of body weight for four days.[27] The possibility that the clinical use of BAL might be contraindicated in some cases of hepatic damage has been raised by the finding that animals with livers damaged by carbon tetrachloride showed toxic signs after doses of BAL that were ordinarily well tolerated.[28] However, BAL has been used in a number of patients with so-called postarsenical hepatitis, and there is no mention of extraordinarily toxic manifestations occurring in these persons.

Although the anticoagulant effect of BAL in vitro is pronounced, doubling the prothrombin time of human plasma, it has not been reported to produce hemorrhagic tendencies in vivo. Fantl and Nance[29] found that rabbits given BAL intramuscularly showed no changes in prothrombin time or coagulation time.

In general, histologic studies of animals receiving both single and repeated doses of BAL have failed to reveal conspicuous morphologic changes except in those dying from acutely lethal doses. Such animals show pulmonary hemorrhages and edema, which are probably the results of the marked vascular action of BAL. Isolated instances of thickening of alveolar walls and renal tubular degeneration have been seen, but it is impossible to correlate these rare findings with the administration of BAL.[28] As noted above, liver damage has been observed to follow large doses.

Action on Man

All clinicians who have written about the therapeutic uses of BAL warn of the undesirable side effects that may occur. Eagle and Magnuson[30] have reported the incidence of toxic manifestations following the intramuscular administration of BAL to 60 normal subjects and 61 patients with arsenical poisoning. At a dose level of 2.5 mg. per kilogram of body weight, less than 1 per cent of injections were followed by mild toxic signs and symptoms. At a level of 4 mg. per kilogram, mild to moderate reactions were noted in about 15 per cent of cases, and at a level of 5 mg., 50 to 60 per cent had reactions. Localized pain at the site of injection was not uncommon, but it was no more severe than that seen after the intramuscular administration of a number of other therapeutic agents. The usual toxic manifestations were nausea, vomiting, headache, burning sensations of the mouth and eyes, lacrimation, profuse salivation, rhinorrhea, muscular aches, tingling of the extremities, sweating of the forehead and hands, pain in the teeth, a sense of constriction in the chest, anxiety and general agitation. Transient elevation of blood pressure was common. The sym toms began about ten to twenty minutes after the injections, reached a maximum in twenty to thirty minutes, and disappeared within fifty to ninety minutes. These findings are in accord with those of Modell et al.,[31] who, in addition, observed that single doses of 8 mg. per kilogram of body weight almost invariably produced marked symptomatology. They also found that doses of 5 mg. per kilogram could be repeated every three hours for twenty-four hours without significant cumulative effects.

Woody and Kometani[32] reported the case of a child who received two overdoses of BAL of 25 mg. per kilogram each. Thirty minutes after the first overdose the child developed anorexia, vomiting and restlessness, all subsiding in an hour. Ten minutes after the second overdose (given three hours later) examination showed cutaneous flushing, mild hyperpyrexia, tachycardia, hypertension, a generalized convulsion lasting for three minutes and coma and stupor lasting for an hour. After the coma the child appeared to be normal, and recovery was uneventful.

Localized abscesses at the site of injection occur occasionally.[30] They seem to occur most frequently in cases of arsenical dermatitis in which the intramuscular needles have passed through infected tissues, and, therefore, are probably the result of secondary infection rather than a direct action of BAL upon the tissues.

Application to the skin can cause varying degrees of localized reactions ranging from mild erythema

to severe whealing and capillary damage.[19] Sulzberger[33] was able to create skin sensitization with repeated applications of a 5 per cent BAL ointment to normal skin. Sixteen of 88 human subjects (19 per cent) developed localized reactions varying from faint erythema with pinhead-sized, papulo-urticarial lesions to marked erythema with confluent urticarial and papular lesions lasting up to five days. These relatively persistent lesions should be distinguished from the erythema and whealing frequently noted after topical application of BAL, which disappear in fifteen minutes to two hours. When applied to skin previously damaged by mustard gas, BAL caused a definite dermatitis in 35 out of 53 subjects (66 per cent).

Epinephrine has been used successfully to alleviate the undesirable side effects of BAL: 0.6 of 1 cc. of 1:1000 epinephrine hydrochloride solution gave rapid and complete relief. Oral or parenteral administration of 25 mg. of ephedrine sulfate half an hour before the administration of BAL prevented the onset of symptoms.[34]

Compounds Related to BAL

Although many compounds related to BAL have been studied, only two are of particular interest — namely, the ethyl ether of BAL and BAL glucoside.

The ethyl ether of BAL is more toxic than BAL. Whereas the initial toxic manifestations of this compound are similar to those produced by BAL, death, when it occurs, is not acute but is almost invariably delayed for days or weeks. Even doses forty times greater than those necessary to produce mild symptoms do not kill immediately. In spite of its comparatively great toxicity the ethyl ether of BAL is of interest because it is more effective than BAL in the treatment of arsine poisoning in animal experiments.[24, 35]

BAL glucoside (BAL-intrav) is much less toxic than BAL and has the advantage of being freely water soluble. Doses as large as 100 mg. per kilogram of body weight have been given intravenously to man without apparent ill effects, whereas BAL itself may produce symptoms when given intramuscularly in doses of 4 mg. per kilogram. Unfortunately, there are not sufficient data to permit a quantitative comparison of the therapeutic activity of BAL glucoside with BAL, but the limited information available suggests that the former has a more satisfactory therapeutic index than the latter.[36-38]

BAL in Specific Poisonings

Although the immediate interest at the time BAL was developed was the treatment of arsenical wargas poisoning, it soon became apparent that the compound was of value in the therapy of arsenical poisoning in general. Investigation of its value in other heavy-metal poisonings indicated that BAL could not be used indiscriminately in the treatment of all because in some cases it not only was valueless but also actually appeared to enhance the toxicity of a metal. The concluding section of this progress report will be devoted to a discussion of the role of BAL in the treatment of specific metal poisonings, and mention will also be made of the effects of BAL on the action of alloxan and phenylthiourea.

(To be concluded)

References

1. Peters, R. A., Stocken, L. A., and Thompson, R. H. S. British anti-lewisite (BAL). *Nature* **156**:616-619, 1945.
2. Waters, L. L., and Stock, C. BAL (British anti-lewisite). *Science* **102**: 601-606, 1945.
3. Barron, E. S. G., Miller, Z. B., and Kalnitsky, G. Oxidation of dithiols. *Biochem. J.* **41**:62-68, 1947.
4. Eagle, H., Magnuson, H. J., and Fleischman, R. Clinical uses of 2,3-dimercaptopropanol (BAL). I. Systemic treatment of experimental arsenic poisoning (mapharsen, lewisite, phenyl arsenoxide) with BAL. *J. Clin. Investigation* **25**:451-466, 1946.
5. Voegtlin, C., Dyer, H. A., and Leonard, C. S. On mechanism of action of arsenic upon protoplasm. *Pub. Health Rep.* **38**:1882-1912, 1923.
6. Walker, E. Chemical constitution and toxicity. *Biochem. J.* **22**:292-305, 1928.
7. Eagle, H. Effect of sulfhydryl compounds on antispirochetal action of arsenic, bismuth and mercury compounds in vitro. *J. Pharmacol. & Exper. Therap.* **66**:436-448, 1939.
8. Szent-Györgyi, A. Action of arsenite on tissue respiration. *Biochem. J.* **24**:1723-1727, 1930.
9. Voegtlin, C., Rosenthal, S. M., and Johnson, J. M. Influence of arsenicals and crystalline glutathione on oxygen consumption of tissues. *Pub. Health Rep.* **46**:339-354, 1931.
10. Rosenthal, S. M. Action of arsenic upon fixed sulphydryl groups of proteins. *Pub. Health Rep.* **47**:241-256, 1932.
11. Peters, R. A., Sinclair, H. M., and Thompson, R. H. S. Analysis of inhibition of pyruvate oxidation by arsenicals in relation to enzyme theory of vesication. *Biochem. J.* **40**:516-524, 1946.
12. Peters, R. A., and Wakelin, R. W. Observations upon relation between sulphydryl groups and pyruvate oxidation in brain tissue. *Biochem. J.* **40**:513-516, 1946.
13. Stocken, L. A., and Thompson, R. H. S. British anti-lewisite. 1. Arsenic derivatives of thiol proteins. *Biochem. J.* **40**:529-535, 1946.
14. *Idem.* British anti-lewisite. 2. Dithiol compounds as antidotes for arsenic. *Biochem. J.* **40**:535-548, 1946.
15. Webb, E. C., and van Heyningen, R. Action of British anti-lewisite (BAL) on enzyme systems. *Biochem. J.* **41**:74-78, 1947.
16. Barron, E. S. G., Miller, Z. B., and Meyer, J. Effect of 2,3-dimercaptopropanol on activity of enzymes and on metabolism of tissues. *Biochem. J.* **41**:78-82, 1947.
17. Young, L. Canadian researches on BAL (British anti-lewisite). *Science* **103**:439, 1946.
18. Peters, R. A., et al. Use of British anti-lewisite containing radioactive sulphur for metabolism investigations. *Biochem. J.* **41**: 370-373, 1947.
19. Sulzberger, M. B., Baer, R. L., and Kanof, A. Clinical uses of 2,3-dimercaptopropanol (BAL). III. Studies on toxicity of BAL on percutaneous and parenteral administration. *J. Clin. Investigation* **25**:474-479, 1946.
20. Adler, F. H., Leopold, I. H., Steele, W. H. S., and Crandall, A. S. Cited by Hughes, W. F., Jr. Clinical uses of 2,3-dimercaptopropanol (BAL). IX. Treatment of lewisite burns of eye with BAL. *J. Clin. Investigation* **25**:541-548, 1946.
21. Wexler, J., et al. Clinical uses of 2,3-dimercaptopropanol (BAL). II. Effect of BAL on excretion of arsenic in normal subjects and after minimal exposure to arsenical smoke. *J. Clin. Investigation* **25**:467-473, 1946.
22. Durlacher, S. H., et al. Toxicological action of 2,3-dimercaptopropanol (BAL). *J. Pharmacol. & Exper. Therap.* (Supp.) **87**:28-32, 1946.
23. Modell, W., Chenoweth, M. B., and Krop, S. Toxicology of 2,3-dimercaptopropanol (BAL) in cats. *J. Pharmacol. & Exper. Therap.* (Supp.) **87**:33-40, 1946.
24. Fitzhugh, O. G., et al. Toxicities of compounds related to BAL (2,3-dimercaptopropanol) with note on their relative therapeutic efficiency. *J. Pharmacol. & Exper. Therap.* (Supp.) **87**:23-27, 1946.
25. Chenoweth, M. B. Cardio-vascular actions of 2,3-dimercaptopropanol (BAL). *J. Pharmacol. & Exper. Therap.* (Supp.) **87**:41-54, 1946.
26. Hitchcock, P. Effect of dithiols and other enzyme inhibitors on blood vessels. *J. Pharmacol. & Exper. Therap.* (Supp.) **87**:55-59, 1946.
27. MacNider, W. de B. Liver injury in dog following use of 2,3-dimercaptopropanol (BAL). *Proc. Soc. Exper. Biol. & Med.* **66**:444-446, 1947.
28. Cameron, Burgess and Trenwith. Cited by Peters et al.[1]
29. Fantl, P., and Nance, M. H. Influence of 2,3-dimercaptopropanol (BAL) on blood coagulation. *Nature, London* **159**:777, 1947.

30. Eagle, H., and Magnuson, H. J. Systemic treatment of 227 cases of arsenic poisoning (encephalitis, dermatitis, blood dyscrasias, jaundice, fever) with 2,3-dimercaptopropanol (BAL). *Am. J. Syph., Gonor. & Ven. Dis.* **30**:420-441, 1946.
31. Modell, W., Gold, H., and Cattell, McK. Clinical uses of 2,3-dimercaptopropanol (BAL). IV. Pharmacologic observations on BAL by intramuscular injection in man. *J. Clin. Investigation* **25**:480-487, 1946.
32. Woody, N. C., and Kometani, J. T. BAL in treatment of arsenic ingestion of children. *Pediatrics* **1**:372-378, 1948.
33. Sulzberger, M. B., Baer, R. L., and Kanof, A. Clinical uses of 2,3-dimercaptopropanol (BAL). V. Skin sensitization to BAL. *J. Clin. Investigation* **25**:488-496, 1946.
34. Tye, M., and Siegel, J. M. Prevention of reaction to BAL. *J. A. M. A.* **134**:1477, 1947.
35. Chenoweth, M. B., Modell, W., and Riker, W. F., Jr. Pharmacology of several dithiols related to 2,3-dimercaptopropanol (BAL). *J. Pharmacol. & Exper. Therap.* (Supp.) **87**:6-22, 1946.
36. Danielli, J. F., Danielli, M., and Mitchell, P. D. Development of chemotherapy for systemic arsenical poisoning. *Nature, London* **157**:217, 1946.
37. Danielli, J. F., et al. BAL-Intrav: new non-toxic thiol for intravenous injection in arsenical poisoning. *Biochem. J.* **41**:325-333, 1947.
38. McCance, R. A., and Widdowson, E. M. Observations on administration of BAL-intrav to man. *Nature, London* **157**:837, 1946.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 34521

PRESENTATION OF CASE

A fifty-five-year-old man entered the hospital because of abdominal cramps and distention.

Three weeks before admission the patient noted the gradual onset of an illness characterized by abdominal swelling and diffuse abdominal cramps. He felt bloated constantly and, in addition, had spasmodic, doubling, abdominal pains, which lasted about a minute and which he could not localize. There was a slight reduction in the number of bowel movements but no change in the character of the stools was noticed. There was no obstipation or passage of bloody, tarry or clay-colored stools. Though the patient's appetite remained good, he ate infrequently because his capacity for food was greatly reduced. A normal-sized meal nauseated him, but he never vomited. The urine was brown as it had been for several years. The legs and ankles became moderately swollen.

The patient had had diabetes for five years. He had been taking 10 units of protamine insulin daily until admission. For three years he had been subject to anginal attacks precipitated by exercise and relieved by nitroglycerin. There had been several episodes of ankle edema, orthopnea and nocturnal dyspnea. He had felt weak and tired since an attack of "virus pneumonia" five months before admission. He thought he had lost weight since that time but did not know how much. About four years before admission he had been jaundiced and felt weakness and malaise for three weeks. There had never been any previous episodes of abdominal symptoms.

The patient's father had died of diabetes, and a brother had the disease.

Physical examination showed a patient who appeared chronically ill and in moderate distress. The skin of the extremities and back had a dusky, cyanotic tinge. The tongue was thickly coated, and the breath fetid. The abdomen was distended, tympanitic and nontender. There were shifting dullness and a fluid wave. No organs or masses were palpable. There was a soft, apical, systolic murmur. The lungs were clear. There was moderate pitting edema extending halfway up the leg, and slight pressural edema.

The temperature was 99°F., the pulse 80, and the respirations 20. The blood pressure was 130 systolic, 70 diastolic.

Examination of the blood disclosed a red-cell count of 4,400,000, with a hemoglobin of 16 gm., and a white-cell count of 8000, with 70 per cent neutrophils. The urine had a specific gravity of 1.012. The sediment was normal, and a test for bile was negative. There was a green sugar reaction. The stools were brown, formed and guaiac negative. The blood chemical values on admission were as follows: sugar 200 mg., nonprotein nitrogen 20 mg., and protein 5.8 gm. per 100 cc.; bilirubin 0.7 mg. per 100 cc. direct, 1.1 mg. indirect; and carbon dioxide 31 milliequiv. and chloride 88 milliequiv. per liter. X-ray studies of the chest and abdomen showed both leaves of the diaphragm to be high, with haziness in the costophrenic sinuses. There was marked gaseous distention of the bowel, which could not be localized but was thought to affect both colon and small bowel. The peritoneal markings were not clear, indicating the presence of the fluid.

In the hospital the patient had a daily temperature between 100 and 102°F. A barium enema on the second hospital day showed delay of retrograde flow in the region of the splenic flexure, though barium passed into the dilated gas-filled and fluid-filled transverse colon. No definite lesion could be made out. The small intestine was also dilated. The urine reaction remained green on 10 units of regular insulin daily. The patient had a shaking chill on the third hospital day.

An exploratory laparotomy was performed on the sixth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. JAMES H. TOWNSEND: May we see the x-ray films?

These x-ray films are very impressive. We were not told about all this tubing, but there it is.

DR. STANLEY M. WYMAN: We have only a few films from the original examination. Some of them were lost, apparently. The heart is definitely enlarged, chiefly toward the left, probably in the region of the left ventricle. The aorta is tortuous, and there is some calcification. There appears to be a small quantity of fluid in the left costophrenic angle and possibly on the right also. The lung fields reveal no definite intrinsic disease. The appearance of the chest is consistent with hypertensive arteriosclerotic heart disease, with probable fluid in both pleural spaces. This film of the abdomen with a Miller–Abbott tube in place was taken the day following the barium enema examination. The barium enema was done with the Miller–Abbott tube in place and quite a way down, as you see from the spot films. The patient was not prepared, and the examination, I gather from the record, was unsatisfactory. The fluoroscopist, in running the barium into the descending colon, arrived at the splenic flexure, where he had difficulty in forcing the barium farther. He took a number of spot films, which show barium passing into the distal transverse colon, where there is considerable fluid and retained material. The spot films of the area reveal no evidence of intrinsic filling defect, no definite kinks and no definite constriction by adhesions. I can say only from the films available that there was delay in the barium column at this point without a definite organic lesion. To go back to the plain film of the abdomen, there is a haziness that suggests fluid in the abdomen. This has to be taken with skepticism because this is a grid film.

DR. TOWNSEND: From the data given I am sure that I shall be unable to make a precise diagnosis. However, there are certain possibilities that I can discuss.

To summarize the positive features, this fifty-five-year-old man, who was known to have had diabetes for five years, had an episode described as jaundice, which I think must always be taken with reservation. Four years before he had had what was called angina. For three years he had had a number of episodes of ankle edema, orthopnea and nocturnal dyspnea. Five months before admission he had what was called "virus pneumonia," and which easily could have been something else, perhaps pulmonary embolism or some other circulatory disturbance in the chest. He was brought to the hospital by an illness of three weeks' duration, characterized by abdominal cramps and swelling of the abdomen and of the ankles, and while in the hospital he had fever.

The physical examination showed a dusky color, apparently cyanosis, although there may have been something else about the color, a coated tongue, definite ascites and fever. From the laboratory evidence there was mild jaundice, elevated plasma bilirubin, both direct and indirect, a slight reduction in serum protein, with a slight alkalosis and slight hypocalcemia, possibly associated with diet. I assume that since this man had cardiac failure he may well have been on a diet low in sodium chloride, which may have a bearing on the chloride of 88 milliequiv. per liter. It is noteworthy that he did not have anemia and that the nonprotein nitrogen was normal. The blood sugar was high enough to prove the diabetes but not strikingly high. He did not have bile demonstrated in the urine. He apparently had normal amounts of bile in the stools. X-ray films suggest fluid in the pleural cavities and in the abdomen and gas-filled loops of bowel, which the x-ray people could not interpret entirely. They could not tell whether the whole intestine was dilated — paralytic ileus — or whether examination showed an obstructing lesion.

What are some of the possibilities? If we try to put them all together and put them on a cardiac basis, there seems little reason to doubt that this fifty-five-year-old man with diabetes had coronary-artery disease manifested by angina pectoris and symptoms of congestive failure. He also had a somewhat enlarged heart, and we wonder if the blood pressure had not been higher in the past than at present. We have no electrocardiographic evidence. I think we might say that he undoubtedly had coronary-artery disease and that he probably had some congestive failure. Could the cardiac condition have led to abdominal symptoms? Could he have had a mesenteric thrombosis or other thrombosis in the abdominal cavity? Yet if he had real mesenteric embolus, such as might come from thrombosis within the heart, one would hardly expect him to live three weeks. The episode would have been much more critical, and he would have died or been in serious trouble within a few hours as a rule. Is there anything about the cardiac condition that might lead to jaundice and ascites? Yes. Jaundice is not common in cardiac failure, although it may occur. Ascites may occur in most types of heart failure associated with right-sided heart failure, such as that seen with adhesive pericarditis or tricuspid lesions or with long-standing, definite, congestive failure, in which the nutmeg type of liver and, possibly, slight jaundice occur. However, this does not sound like that sort of history.

Are there any abdominal conditions that are part and parcel of the diabetes? There are at least three types of abdominal conditions that can produce abdominal symptoms and have diabetes as a feature. One is chronic pancreatitis, with enough destruction of islet tissue to produce diabetes, and I think it is possible that this patient could have had chronic recurrent pancreatitis. Jaundice and ascites can occur with it. This is a possibility, but I can see no way to prove it. The second abdominal condition associated with diabetes is a special form of liver cirrhosis, pigment cirrhosis. Hemochroma-

tosis is associated with diabetes, usually from pancreatic fibrosis from pigment. This is seldom associated with jaundice, but I recall a case given to me a year or so ago in which four years before death the patient showed evidence of cirrhosis, including jaundice and ascites, and at that time on biopsy showed early Laennec's cirrhosis. Four years later, at the time of death from liver failure, there were extensive pigment deposits of the type called hemochromatosis. That is a possibility, but we have very little evidence, and I do not see how one can make the diagnosis.

Another possibility is cholesterol disease. We are not given the value of the blood cholesterol, but there is a condition of hypercholesterolemia, which can be associated with deposits of cholesterol with fibrosis in the pancreas sufficient to cause diabetes. This also may be associated with enlarged liver and occasionally with jaundice. However, I doubt very much that it would lead to ascites; at least, I have never seen it. It can also be associated with coronary-artery disease and frequently terminates with coronary thrombosis.

What other possibilities should we consider? Ordinary liver cirrhosis, I think, is entirely possible. We are not given the usual battery of liver tests. We are told nothing about the prothrombin time, the cephalin flocculation test or the phosphatase level. We do know that he had ascites and jaundice, and that combination is always suggestive of Laennec's cirrhosis of the liver.

What about gallstones? There is a history of an attack of jaundice, without pain, four years ago. This time there were pain and jaundice. However, there seems to be very little to suggest that the patient was troubled with cholelithiasis, and it would be rather hard to explain the terminal picture on that basis.

What about the possibility of carcinoma of the pancreas? I think the possibility of neoplasm in the last few weeks of his life cannot be excluded. It could have been in the pancreas (it can be almost anywhere). I doubt that there is sufficient evidence to make a diagnosis without looking inside, which we are going to do vicariously in a minute.

One other possibility: Could he have had a spontaneous thrombosis of some radicle of the portal vein? Such things do occur. They are very difficult to diagnose in life and very apt to be associated with crampy, abdominal pain of indefinite character. They can be rapidly followed by the development of ascites and edema and large enough to result in a large area of gangrene of the bowel, but this man would not have lived three weeks if that had occurred. Of all possibilities, I think this is the least likely. If I were to list my diagnoses, I would say, of course, diabetes mellitus, coronary-artery disease and, I think, intra-abdominal thrombosis, probably in the portal system, possibly in some way related to cirrhosis of the liver.

DR. WILLIAM DOCK: I think these dusky legs make one think of hemochromatosis. That is an odd thing to have — cyanosis of the legs — without cyanosis of the lips, ears and fingers. With cyanosis of the back and legs it sounds as if he may have had an odd color, not merely diabetes with cyanosis, and it makes one suspicious. I think it is an important point. Patients with cirrhosis occasionally have bouts of fever and abdominal conditions unexplained by positive blood cultures or anything else. It may be that there was some intercurrent disease. However, I think this is a case in which terminal pylephlebitis ought to be thought of. I should think he might have had carcinoma in the tail of the pancreas. I would be inclined to guess that he had bronze diabetes and got into new troubles superimposed on his cirrhosis, so that he came in on the Surgical rather than the Medical Service.

CLINICAL DIAGNOSES

Large bowel obstruction,? carcinoma.
Diabetes mellitus.
Angina pectoris.

DR. TOWNSEND'S DIAGNOSES

Diabetes mellitus.
Coronary-artery disease.
Cirrhosis of liver.
Intra-abdominal thrombosis.

ANATOMICAL DIAGNOSES

Hemochromatosis, liver, pancreas, skin and lymph nodes.
Hepatoma, with extension into hepatic and portal veins.
Esophageal varices.
Ascites.
Splenomegaly.
Operations: exploratory laparotomy; bilateral femoral-vein ligation.
Thrombosis, left common femoral vein.
Hydrothorax.
Pulmonary congestion.
Chronic cholecystitis.

PATHOLOGICAL DISCUSSION

DR. JOHN B. STANBURY: The patient did come in on the Surgical Service. It was thought when he was first seen that there was distention of the small bowel, and enough possibility of small-bowel obstruction to justify surgical exploration. That was done. No obstruction was found, but a nodular liver was observed from which a biopsy was taken. It showed a marked grade of cirrhosis with a great deal of hemosiderin deposit, and a diagnosis of hemochromatosis was made. The patient was then transferred to the Medical Service, and the prognosis seemed so hopeless that they were not very

much interested in doing any great battery of liver-function tests. The bromsulfalein test showed 40 per cent retention of the dye, and the thymol turbidity was 7 units.

DR. TRACY B. MALLORY: The patient died in two weeks. There was an episode suggesting pulmonary embolism following which the leg veins were ligated on both sides. From that time on there was constant seepage of fluid through the wounds where the veins had been ligated that could not be stopped. The peritoneal fluid evacuated at operation reaccumulated rapidly.

At autopsy we found that the liver weighed 3400 gm. and was very grossly nodular, with two types of nodules, quite sharply distinct in color. In cutting across the liver we found in the central portion a large tumor similar in appearance and color to one of the types of nodules. Also, many thrombi were found in both the hepatic and portal veins. So the diagnosis of primary hepatoma with invasion of the venous system of the liver was made. There was also a thrombotic occlusion of the portal vein behind the tumor thrombus. There was moderate involvement of the adrenal glands and pancreas, and the lymph nodes in the porta hepatis were deeply pigmented.

DR. TOWNSEND: Was any reason found for the rather sudden decline of the patient three weeks before entry?

DR. MALLORY: I imagine that represents the rapid progress of the hepatic carcinoma, which spread very quickly throughout the venous system of the liver.

DR. TOWNSEND: Do you often find hepatic carcinoma developing on the basis of hemochromatosis?

DR. MALLORY: I have the impression that I have seen it disproportionately often in hemochromatosis. I have seen figures saying that that is not so. Considering the rarity of hemochromatosis, I think a surprising number of patients die with hepatoma.

DR. JOHN B. QUINBY: What did the heart show?

DR. MALLORY: Mild atherosclerosis of the coronary arteries without narrowing and no infarction. The kidneys showed nothing remarkable.

CASE 34522*

PRESENTATION OF CASE

First admission. A fifty-one-year-old unmarried woman was admitted to the hospital because of severe epigastric pain. A diagnosis of gall-bladder disease was made. The symptoms subsided almost completely, and she was discharged on the fifth hospital day.

Fourth admission (four years later). In the interval the patient had two admissions for recurrent bouts of epigastric pain. During the last she underwent an exploratory laparotomy and appendectomy. The abdominal organs, including the gall bladder, were grossly normal. During this admission the patient was found to have an adenocarcinoma of the sigmoid colon, and a Mikulicz operation was subsequently done. She was discharged on the sixty-second hospital day.

Seventh admission (approximately twelve years later). In the interval the patient had been admitted on two separate occasions for a ventral hernia and for closure of the colostomy wound, the last admission being ten years before this one. At this time she was admitted because of increasing difficulty in swallowing and some weight loss. A roentgenogram showed findings consistent with carcinoma of the lower third of the esophagus. A biopsy showed epidermoid carcinoma, grade III. An esophagectomy and esophagogastrostomy were done, and the patient discharged on the forty-third hospital day.

Eighth admission (seven years later). In the interval the patient had been seen more or less regularly in the Tumor Clinic, and no evidence of recurrence of either the esophageal or the sigmoid cancer noted. Approximately one month before admission she began to have frequent attacks of sharp, stabbing pain in the right upper quadrant. This pain was severe and accompanied by nausea, vomiting and gaseous eructations. The pain radiated to the back but not into the shoulder. She denied any change in the stools or urine but admitted to being jaundiced with several of the attacks. The present episode had begun four days before admission.

Physical examination revealed a poorly nourished woman in no acute discomfort. The scleras and skin were questionably icteric. The lungs were clear. The abdomen was flat, and numerous dilated veins were seen coursing under the skin. There appeared to be a considerable amount of voluntary spasm. The right upper quadrant was tender to deep palpation, but neither liver nor gall bladder could be felt. The spleen was not palpable.

*Presented at a meeting of the New England Cancer Society held at the Massachusetts General Hospital.

Laboratory study revealed a serum van den Bergh of 1.8 mg. per 100 cc. direct and 2.0 mg. per 100 cc. indirect and an amylase of 116 units per 100 cc. The hemoglobin was 11 gm., and the white-cell count 6000. The specific gravity of the urine was 1.003, but examination was otherwise negative.

In the hospital the patient had another acute attack of pain, from which she was allowed to recover before operation. In the meantime she was given penicillin, streptomycin and three blood transfusions. On the twelfth hospital day a cholecystectomy and choledochostomy were done. One large and several small stones were found in the common duct, which was noted to be very large but soft. She convalesced well and was discharged on the tenth postoperative day. A cholangiogram done two days before discharge showed good filling of the biliary radicles, both intrahepatic and extrahepatic. There was some dilatation of the whole system, but the dye passed readily into the duodenum.

Final admission (two months later). In the interval the patient had been followed in the clinic and was very well when last seen, approximately six weeks before the present admission. She had continued to be up and about feeling well until two days before admission, when she noted the onset of anorexia and abdominal discomfort. On the following day she went to bed and had nausea and vomiting of blood of an unknown amount. She was also said to have passed blood by rectum. On the morning of the day of admission she was found unresponsive. It was also noted that the skin was yellowish. She was admitted in a state of coma.

Physical examination revealed a comatose, emaciated woman breathing heavily. The skin and conjunctivas showed jaundice. The lungs were clear. Abdominal and neurologic examinations were essentially negative. Rectal examination was negative. The temperature was 98.6°F., the pulse 100, and the respirations 20. The blood pressure was 130 systolic, 90 diastolic.

Laboratory examination revealed a serum van den Bergh of 8.5 mg. per 100 cc. direct and over 12.5 mg. per 100 cc. indirect and a nonprotein nitrogen of 42 mg. per 100 cc. The carbon dioxide was 22 milliequiv. per liter, and the sugar 76 mg. per 100 cc. Determination of the prothrombin time was attempted, but the blood did not clot even after 120 seconds with a control of 16 seconds. The hemoglobin was 15 gm., and the white-cell count 9000, with 81 per cent neutrophils. The urine showed a ++ test for bile. A stool was guaiac negative.

On the following morning the patient's respirations were more rapid, and the jaundice deeper. Later that day respirations ceased, and she died.

Differential Diagnosis

Dr. Grantley W. Taylor: This is an extraordinary case. There are several points of considerable interest. First of all, this woman had a carcinoma of the colon at the age of fifty-five, which was cured apparently. At the age of sixty-seven she entered again with a carcinoma of the esophagus, which was an epidermoid, Grade III. This must represent one of the rare, very early cures of carcinoma of the esophagus because seven years later, when the gall bladder was operated on, I think it would have been remarked if she had shown any evidence of intra-abdominal extension or recurrence of carcinoma. She lived long enough to justify the original diagnosis of gall-bladder disease because when she came back on the eighth admission she had gallstones.

When the patient came in on the eighth admission she was a sick woman with frequent attacks of sharp pain, nausea, vomiting, gaseous eructations and questionable icterus, and she was in poor shape. The only extraordinary thing in this admission is the amylase of 116 units, which, if true, is certainly extreme. It makes one wonder if she had pancreatitis. Pancreatitis is certainly an overwhelming disease. She had an attack of pain but was not in any acute discomfort, and I am inclined to think that the amylase determination was an error. She was treated with penicillin, streptomycin and blood transfusions — again, a method of therapy consistent with the assumption that she had pancreatitis or something of that sort. Nothing was done until the twelfth day, when gallstones were removed and the common duct drained. A cholangiogram was done before discharge, which means that she had a T-tube in place and the idea was to carry out a protracted drainage of the biliary tree. That is what I get out of it. At readmission nothing is said about a biliary sinus or a biliary catheter. However, she was followed in the Out-Patient Department and did very well until just before the final admission, when she had an overwhelming onset of the final illness — an episode of anorexia, abdominal discomfort, nausea, vomiting and bleeding by rectum — and lapsed within two days into a state of

coma. On examination she was breathing heavily and was jaundiced. Obviously she had severe derangement of the bleeding tendency when she came back because the blood taken for prothrombin time did not clot, even after two hours. The blood hemoglobin was 15 gm., perhaps owing to hemoconcentration. The white-cell count was normal, the urine showed bile, and the stool was guaiac negative — a contradiction to the history of hematemesis and melena.

As I studied this case the question was obviously whether or not this was a complication of the former carcinoma in the form of hepatic metastases. It seems extremely unlikely that two months after cholecystectomy, at which time presumably the liver was not manifesting hepatic metastases, metastatic disease involving the liver from either of the previous carcinomas would occur. Of course the interesting thing is how rarely we see jaundice in cases of metastases involving the liver. Then the question is whether she was suffering from a complication of the cholecystectomy. We have been known to injure the common duct, even in this hospital, so that she could very well have had such a complication. Against that is the fact that following cholecystectomy she did well for two months. The terminal illness was abrupt — two days — and of severe onset. Were one large and several small stones removed and one that descended to cause another acute episode of obstructive mechanical jaundice left? I think that is rather unlikely. The lapse of the patient into coma, with a protracted prothrombin time such as that described here, sounds to me as if she had a profound visceral derangement of the liver, and that the terminal episode was one of liver failure — due to what, I cannot tell you. It is consistent with severe hepatitis or acute yellow atrophy or something of that sort.

What else could she have had? A hemorrhagic pancreatitis? At the final episode she complained of anorexia and of abdominal discomfort but nothing suggestive of the overwhelming onset of abdominal distress of pancreatic apoplexy. That is as far as I can go.

Dr. George Levene: Is the pain radiating back into the shoulder suggestive of pancreatitis?

Dr. Taylor: On the eighth admission she probably had something for which she was kept in the hospital for twelve days and given penicillin, streptomycin and transfusions. We have very few data given here, but everything was normal except for the elevated amylase. It must have been thought that she had a pancreatitis secondary to biliary-tract disease because biliary drainage was instituted, a T-tube put in place and a cholangiogram taken before she went home. Nothing is said about the state of the pancreas or the abdominal findings.

Dr. Louis P. Hastings: Dr. Taylor, did she have plasma transfusions a few months previously? What is the possibility of homologous serum hepatitis here?

Dr. Taylor: I think it is possible. We know that some of these patients have tremendously severe jaundice supervening on that basis. We certainly do not expect it with transfusion of whole blood as commonly as we do with plasma.

Clinical Diagnosis

Homologous serum hepatitis.

Dr. Taylor's Diagnosis

Hepatitis, with liver failure.

Anatomical Diagnosis

Homologous serum hepatitis.

Pathological Discussion

Dr. Benjamin Castleman: At autopsy this patient had a very small liver, weighing 700 gm.; it was soft, flabby, and brownish red, more so on the right side, with small, yellowish to grayish-white areas here and there. These grayish-white areas represented portal areas, and the reddish-brown areas represented the central parts of the lobule. In the central parts of the lobule the liver cells were wiped out completely and replaced by blood. This case represents an acute hepatitis of a fulminant variety and quite consistent with homologous serum jaundice. The patient had received three transfusions, and I have asked Dr. Soutter, who is in charge of the Blood Bank, to comment on the possible causes of the hepatitis.

Dr. Lamar Soutter: This case was of great interest to us because of our desire to avoid this complication. The possible source of homologous serum jaundice could have been from a needle or from a transfusion. For the past half year, at least, all hypodermic and intravenous needles in the hospital have been autoclaved so that the possibility of receiving hepatitis from another patient through the means of the needle is almost nonexistent. In

this case the other possible source is the transfusions. Out of 50,000 whole-blood transfusions from our Blood Bank this is the first case of homologous jaundice. Undoubtedly, there may be others in which the diagnosis was not made or the patient had a light case of jaundice not attributed to this source. It is possible for a person to have hepatitis or jaundice and not know about it — or not remember about it. We do not have any idea how long one is capable of carrying the virus before transmitting it to someone else. We do know that the incidence of homologous serum jaundice following whole-blood transfusion is infrequent as compared with that after dry plasma.

We investigated the donors of the three transfusions in this case. The first donor was a Negro boy, a professional donor of this hospital. He had been used before, and I am sure, after questioning him carefully, that he had no knowledge of ever having had any disease similar to jaundice or hepatitis. The second donor was a Red Cross volunteer, whose blood was sent to us by the Red Cross. I talked to him and found that there was no history of hepatitis or jaundice. The third blood came from an institution that establishes a credit in this hospital from which it can draw blood when needed. Unfortunately, although we believed that that institution had standards comparable to our own and observed the state and federal regulations regarding histories and physical examinations for donors, we found that it had collected blood at a prison but had neglected these matters. We assume that the blood that infected this patient came from that source, but of course there is no proof. The moral is obvious — a careful screening of donors must take place to keep down the incidence of the disease. I do not mean screening by the mere process of a technician asking the donor if he has had jaundice. But if a doctor will ask the donor if he has had "yellow jaundice" of the skin or scleras and will go into the symptoms of hepatitis, we may cut down on this unfortunate complication.

Dr. Richard B. Cattell: Dr. Castleman, have you ever observed this same picture in the liver in deaths following extensive disease with long common-duct obstruction due to stone?

Dr. Castleman: No, we never see it with stones. The liver, if involved, would be large, not small.

Dr. Cattell: I mean following operation for common-duct stones.

Dr. Castleman: Not so rapidly as this. The patient died within three days of the onset of symptoms. It was a fulminating form of liver disease. I do not believe I have seen obstruction that fast. Have you?

Dr. Cattell: No.

Dr. John Fallon: What did you find in the pancreas?

Dr. Castleman: Nothing. The common duct was not dilated, and there were no residual stones.

Dr. Taylor: The tube had been taken out after the final cholecystogram?

Dr. Castleman: Yes. A note was made to that effect in the Out-Patient Department record.

Dr. Taylor: I did not make out why, on the eighth admission, the patient was kept for twelve days on penicillin, streptomycin and transfusions — in preparation for a gall-bladder operation.

Dr. Castleman: It was thought that she had acute cholecystitis. She was very sick before operation.

Dr. Soutter: The cardiologists spent five days getting her ready for operation.

The New England
Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established 1828

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE COMMITTEE ON PUBLICATIONS

Richard M. Smith, M.D., *Chairman*
James P. O'Hare, M.D. Conrad Wesselhoeft, M.D.
Oliver Cope, M.D. John Fallon, M.D.

Joseph Garland, M.D., EDITOR

ASSOCIATE EDITORS
Thomas H. Lanman, M.D. Donald Munro, M.D.
Henry Jackson, Jr., M.D.

Clara D. Davies, EXECUTIVE EDITOR
Robert O'Leary, ASSISTANT EDITOR

EDITORIAL BOARD
C. Guy Lane, M.D. Maxwell Finland, M.D.
Henry R. Viets, M.D. James M. Faulkner, M.D.
Robert M. Green, M.D. Carroll B. Larson, M.D.
Dwight O'Hara, M.D. Francis D. Moore, M.D.
Fletcher H. Colby, M.D. C. Stuart Welch, M.D.
Robert L. Goodale, M.D. Vernon P. Williams, M.D.
Chester M. Jones, M.D. Benjamin Castleman, M.D.
Harvey R. Morrison, M.D. Hugh R. Leavell, M.D.

SUBSCRIPTION TERMS: $7.00 per year in advance, postage paid, for the United States (medical students, $4.00 per year); Canada, $8.00 per year (Boston funds); $9.50 per year for all foreign countries belonging to the Postal Union.

MATERIAL should be received not later than noon on Thursday, three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS, *including those concerning classified advertising but not those regarding other advertising*, should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

NEW ENGLAND ADVERTISING REPRESENTATIVE (*except for classified advertising*): Edwin B. Tyler, 89 State Street, Boston, Massachusetts. Telephone LA 3-5516.

IN UNION STRENGTH

THE proposal of the Blue Cross and Blue Shield plans to form a joint national association for more effective interstate operation has met with vigorous though not unexpected opposition. The proposed organization, under the name of Blue Cross-Blue Shield Association, Inc., was to have been a nonprofit membership corporation for the purpose of providing mechanisms for facilitating plan enrollment activities, collecting and interpreting experience data for all plans, basic underwriting and actuarial service for all plans, and the organization of Blue Cross-Blue Shield Health Service, Inc., as a stock insurance company. The object of the Health Service was to furnish coverage to employees of national firms where approved plans do not exist, and excess coverage where necessary; a central agency through which enrollment, billing and collection could be handled for nationally enrolled groups; uniform rates and benefits for all employees of nationally enrolled groups regardless of place of residence; and uniform regulations regarding enrollment, membership and administration of benefits. These provisions were to provide its sole purpose for existence.

Opposition to it was based on the fear that in union there is too much strength, that centralization of organization entails centralization of authority, that this country's cherished heritage of free enterprise would be placed in jeopardy, and that an organization for the control of medical practice would be ready at hand for the Government to take over at will.

Here there was present the usual basis of controversy — not between clear right and clear wrong — but between two arguments, each of which contains or seems to contain points in its favor.

Despite the dangers that were so clearly set forth by the opponents of the proposed association, it had to be borne in mind by the medical profession that the probable alternative to the acceptance of some larger and well organized voluntary prepayment plan for medical service would be a determined attempt at Government control as outlined in Mr. Ewing's recently publicized ten-year program. It seemed also apparent to many observers of modern political trends that the motto *E pluribus unum*, adopted at one time with a reasonable show of enthusiasm, may still have its virtue. The remark attributed to Benjamin Franklin after the signing of the Declaration of Independence that the signers would do well to hang together unless they wanted to hang separately indicates only that the advantages of united effort may sometimes outweigh its disadvantages.

The Blue Cross and Blue Shield Commissions were directed by the Los Angeles Conference of Blue Cross and Blue Shield plans in April, 1948, to revise the original proposals for a national association and submit them to the conference of plans to be held in October at French Lick Springs. This was done; the Blue Shield plans voted to submit the whole matter to the House of Delegates at its

meeting this month at St. Louis, and the Blue Cross voted to adopt the proposals but to defer action until after the same meeting.

The House of Delegates, giving as a main reason for its decision the possibility of Department of Justice action against a national company, voted to disapprove the association, favoring instead a national enrollment agency to co-operate in co-ordinating all prepaid health insurance plans. Such an agency would not be limited to sponsoring Blue Cross and Blue Shield plans alone.

The clear duty of the physicians of the country is now to support the actions and the decisions of their representative body, disregarding any differences of opinion that may previously have existed. The problems that lie ahead can be satisfactorily solved only by complete co-operation, and by recognition of the authority with which the House of Delegates of necessity speaks.

"FORSAKE NOT THYSELF"

THREE moral obligations implicit in the ministry of the physician are the subject of Dean Willard L. Sperry's talk before the staff of the Massachusetts General Hospital, published elsewhere in this issue of the *Journal*; they concern the practice of medicine, but they present also logical points of contact with the profession of ministering to the mind and to the soul. They are: to tell the truth, but so kindly that silence may sometimes take the place of words; to maintain at all times a sense of the sacredness of life; and to consider the individual at the expense of that abstraction known as mass man.

Judgment, as Hippocrates said, is difficult, and often the definition of a problem may be more stubborn than its answer. Moral judgments in particular may be relative, and the right of yesterday may be the wrong of today. Ethics can quickly change for the worse as well as for the better, and the change can be easily accepted, as was shockingly demonstrated during the years of Hitler's leadership in Germany. The principle of conscience, however, according to Dean Sperry's thesis "has an absolute warrant" and cannot change.

Often the moral choice that confronts the physician is not between black and white, where the just course is plainly marked, but between two shades of gray. Having chosen what seems to be the lighter shade he must go ahead "on the assumption that it becomes . . . a clear white." Tragedy is not a matter of a conflict between good and evil, but "a matter of a collision of two loyalties, each of which is wholly good on its own ground." This conflict has been tersely phrased by Richard Lovelace, whom Dean Sperry quotes:

> "I could not love thee, dear, so much,
> Loved I not honour more."

The ethics of truth-telling must be tempered with discrimination. Falsehood is not to be condoned, but as a matter of mercy and of what might be called the greater honesty, the absolute truth, or what it seems to be, may sometimes need to be withheld. Time, too, may suddenly so change the apparent facts that what was held to be the truth becomes an error.

The problem of euthanasia does not immediately or openly concern the physician, but it involves a principle on which he must take his stand. This must be settled for the physician as for the minister on the basis of a profound reverence for life. A deviation on the part of medicine from its basic principle of saving life must constitute a crack in its armor. "If we forfeit that reverence we have slipped our moral moorings . . . it is not our business to take life, only to try to save it."

In the face of mass evaluations of strong nationalistic and group trends, of the principle of the greatest good to the greatest number, the physician in partnership with the minister must continue to have faith in the value of the individual.

THE MEDICOLEGAL DEATH

FEW physicians, in all probability, are entirely clear in their minds as to the exact nature of their obligations to the state in the matter of death reports. Their medicolegal obligations, at least so far as these relations in the Commonwealth of Massachusetts are concerned, are admirably presented in the article by Ford published elsewhere in this issue of the *Journal*.

Certain categories of death, as set forth, must come under the jurisdiction of the medical examiner. These and certain others — hospital deaths within twenty-four hours of admission, hospital deaths when the decedent was unconscious on admission and remained so, any death pronounced by a physician other than the attending physician and any death when the patient was not attended by a physician within two weeks — must be reported to the medical examiner for his decision as to jurisdiction.

Deaths so reported in which the medical examiner declines authority may be certified by the attending physician if he is available and attended the decedent at least twice, one of which visits was within two weeks of death. Otherwise the board-of-health physician may make the certification.

The interest of the public is in discovering and solving crime and in protecting the public health where it may be endangered by virulent communicable disease, by industrial hazards or otherwise.

The friction that sometimes exists in metropolitan areas between the resident staffs of hospitals and the medical examiner's office over the performance of autopsies could be largely eliminated by a proper understanding by the former of the duties of the latter. These difficulties could largely be eliminated, as Dr. Ford says, "if each hospital were to designate a single physician with the experience and authority necessary to ensure complete and accurate reporting of medicolegal deaths and to facilitate the prompt viewing of bodies at the hospital." If this were done, more cases would be available for hospital autopsy.

THE WASHINGTONIAN HOSPITAL

In spite of many difficulties, the Washingtonian Hospital is carrying on. As the oldest hospital of its kind in the United States, it is continuing to make its contribution to the treatment of alcoholism. Because of its obscure location and quiet work, few people realize that behind its ancient façade patients with acute and chronic alcoholism are continuously being treated by psychotherapy and reflex conditioning. Alumni of the hospital have formed a "conditioning club" that meets semimonthly for group therapy with the medical director.

Last year 941 inpatients and 106 outpatients were given treatment. The average daily census is about 25. The bed capacity is 35.

Since its reorganization some ten years ago, it has continued its relation with the Community Fund. It maintains friendly relations with the Alcoholics Anonymous groups, but its main support comes from patients referred for treatment by private practitioners.

The Washingtonian Hospital, an institutional member of the American Hospital Association, is unique in offering the following services: treatment of acute alcoholic psychoses, acute intoxication without psychoses, cirrhosis of the liver, alcoholic neuritis, vitamin deficiency and malnutrition. It also institutes withdrawal procedures for certain alcohol and drug addicts. Other functions emphasized are efforts to rehabilitate alcohol addicts by psychotherapy, including some patients who require part-time hospitalization with working arrangements and social case work. Public education through addresses given to professional and lay groups is also emphasized. Consultative advice to social agencies and community leaders interested in problem drinkers is given.

In spite of the rising costs of medical care, the hospital is carrying on, mainly because a real need for it exists and because physicians practicing in Massachusetts know of its long service record and the accomplishments it has demonstrated in this uphill work.

MEDICOLEGAL ABSTRACT

Liability for Malpractice — Administration of narcotics. A recent Massachusetts case involved questions of such general interest in connection with the liability of physicians for their administration of narcotics that a brief was filed in the case in behalf of the Massachusetts Medical Society.

The testimony in the case was wholly contradictory on the essential questions of how much morphine was given and under what circumstances it was given. The evidence in its aspect most favorable to the patient, who sued the doctor, was that on December 25, 1939, she was suffering from

nausea but without pain; that the defendant, without any complaint of pain by her and without any physical examination or questions regarding medical history, gave her a hypodermic injection of morphine, which was repeated twice that day; that early in 1940 the defendant gave her another injection in similar circumstances; that in 1941 the defendant gave her occasional injections until by July she was receiving about two injections a week; that by the end of August he was giving her an injection every day, in September twice a day, and in October three times or more a day until the patient's husband ordered the defendant from the house and threatened to "clean him up"; that thereafter the patient became "jumpy and nervous"; and that two days later, after telephoning about every doctor in the town for morphine, the patient experienced a complete black-out and was taken to a hospital suffering from morphine addiction and described as "one-quarter of the way along to confirmed addiction." The patient testified in effect that she had never stated that she had pain until after the defendant had ceased giving her the injections. There was medical testimony that it was not proper medical practice to administer morphine to a patient who complained of nausea but not of pain, or over a period in which there was no pain involved, or to continue giving morphine in the absence of a diagnosis of a condition that could not be cured.

There was evidence that another physician had given the patient codeine from 1939 on and during the period in which the defendant was treating her. There was also evidence that the patient had taken quantities of phenobarbital at some time, although it was not shown that she had taken phenobarbital during the period when she was receiving frequent injections of morphine from the defendant. Therefore, the question was presented whether the patient's condition when she was taken to the hospital was caused by morphine administered by the defendant or by other drugs. The court held that there was ample evidence, presumably the diagnosis of her condition as morphine addiction, to indicate that her condition was proximately caused by morphine administered by the defendant.

The court does not explain in what sense the injections given by the defendant caused the patient's condition. The court presumably meant that the jury could have believed that the injections given by the defendant were sufficient by themselves to account for the patient's condition or that the defendant's treatments would have caused some kind of breakdown by themselves although the patient's condition may have been aggravated by the codeine and phenobarbital. There is a sense in which a doctor may be said to have caused an addiction if his patient merely learns to like the effect of a drug from his injections, and the patient, afterward satisfying her taste from other sources, becomes an addict. The court apparently did not regard the case before it as such a case, and it did not decide what rule should be applied in such a case.

The defendant argued that the plaintiff sought the morphine she got from him, knowing the risks involved and voluntarily assuming them. The court did not deny that she would be barred from recovery if such testimony were true but rejected this argument for the reason that on the evidence the jury could have found that she did not know or assume the risks. The plaintiff herself testified that if not at first, at least eventually, she sought the injections she received from the defendant. She testified that by about the last of July, 1944, she was "beginning to get a little sneaky — starting to lie" and did not always tell the defendant the truth about her condition. She testified that she did not know what the defendant was giving her, although in July she had a "suspicion," and she knew that it was something that was relieving her and making her feel "pretty high." The court concluded:

> From this, together with other evidence that need not be stated, the jury could have found that she knew she was getting morphine, but they were not obliged so to find. Much less were they obliged to find that she knew at what point addiction would begin, or that at any time before addiction became a fact she had ceased to rely upon the superior knowledge of the defendant as to the amount of the drug that could safely be taken over a given period of time. There was medical evidence that a person could become addicted "without knowing it."

The court plainly implied that after addiction has become a fact the patient might not be wholly responsible for her actions in attempting to get morphine injections and might not be barred from recovery on the ground that she assumed the risks. It is obvious in this case that when the patient started lying to the defendant to obtain morphine injections she had ceased to rely on the superior knowledge of the defendant and begun to assume the risks herself. The court must have thought that the jury could find that this was after the addiction was a fact. The time of addiction, therefore, becomes an important issue in cases such as this.

It was argued in the case that the patient by "lying" to obtain morphine injections was guilty of a criminal offense, which should prevent her from holding the doctor liable. However, the court held that the statute, which applied only to lying "for the purpose of procuring a prescription for, or the delivery of, a narcotic drug," was not applicable to a case of misrepresentation for the purpose of obtaining an injection personally administered by the doctor, such an injection not being a "delivery" within the meaning of the statute.

The court held that on this evidence, the jury could render a verdict for the plaintiff, even if they need not have done so. Reassuring the medical profession the court said:

> This decision rests upon evidence of improper and unprofessional conduct on the part of the defendant leading to addiction in the plaintiff. . . . Nothing contained herein need cause anxiety to an honest physician who administers narcotics to a patient in accordance with the prevailing standards of medical practice.

This reassurance must be read in the light of the practical difficulties of proof that may be involved. In any case an honest doctor takes the risk that his testimony may not be believed. For example, in the case before the court, if the defendant's records and testimony had been believed, he would have appeared to be an honest physician administering narcotics to a patient in accordance with the prevailing standards of medical practice. The jury, however, apparently believed the patient's testimony, and this required the court to view the defendant's conduct in a different light. (*King* v. *Solomon*, 1948 Mass. Adv. Sh. 1005.)

CORRESPONDENCE

UNIVERSITY OF ROCHESTER TRAINING PROGRAM IN PSYCHOTHERAPY

To the Editor: I have read with great interest the article entitled "Medical Schools and the Quality of Medical Care," by Dr. E. Richard Weinerman, which appeared in the November 25 issue of the *Journal*. I think that you are doing the profession a great service by publishing articles (and editorials!) on the subject of modern medical training and its socio-economic aspects. This is a timely reminder for those of us who, as students, find ourselves confronted with a maze of material in clinical medicine and who may therefore lose sight of the other implications of disease.

Nevertheless, for the sake of the record, I should like to point out that at the University of Rochester, under the expert guidance of Dr. John Romano, a well integrated program of training in psychotherapy has been initiated. This program began two years ago and now applies to students in all years. A new building has recently been erected for the hospitalization of patients with mental illness, and students in their third and fourth years are receiving intensive training in this new clinic. The course given here not only includes the study of basic psychiatry but also considers the ancillary disciplines of sociology and economics, as presented in lectures by persons who head the social service at the Strong Memorial Hospital.

Most of the students realize the great importance of this aspect of medical training — and not only of medical training, but of medical living and thinking, if I may call it that.

Articles like Dr. Weinerman's are therefore highly welcome and I hope that others on this vital topic will be forthcoming in your splendid *Journal*.

Ernest L. Levinger
Third-Year Student
University of Rochester School of Medicine

BOOK REVIEWS

Unipolar Lead Electrocardiography*: *Including standard leads, unipolar extremity leads and multiple unipolar precordial leads. By Emanuel Goldberger, B.S., M.D. 8°, cloth, 182 pp., with 88 illustrations. Philadelphia: Lea and Febiger, 1947. $4.00.

Dr. Goldberger's book is really the first devoted almost exclusively to the subject of unipolar leads. Although these leads were studied and described by Wilson many years ago, they have come into general use only recently. The literature on this subject is growing rapidly but there has been a real need for a textbook to explain the theory and define the uses and limitations of unipolar leads. Dr. Goldberger's book fills this requirement in part.

The presentation of material is an orderly one, beginning with an explanation of underlying theory, continuing with detailed instructions for taking leads and ending with a discussion of their clinical application.

Reasonable objections can be raised to the rather dogmatic way in which the subject matter is presented. Nevertheless, the book serves a very useful function in placing proper emphasis upon the origin of extremity lead patterns from basic patterns in the heart itself. Dr. Goldberger's approach also serves to emphasize heart position in relation to the recording electrodes. This represents another step away from purely empirical interpretation even though one does not agree with every statement the author makes. This monograph is not intended as a complete textbook, and therefore detailed evaluations of unipolar leads cannot be expected. This book is recommended to all who are interested in electrocardiography.

The Epithelia of Woman's Reproductive Organs*: *A correlative study of cyclic changes. By George N. Papanicolaou, M.D., Ph.D., Herbert F. Traut, M.D., and Andrew A. Marchetti, M.D. 4°, cloth, 53 pp., with 22 plates. New York: The Commonwealth Fund, 1948. $10.00.

This monograph records a decade of painstaking correlative research at Cornell University Medical College, sponsored by the Commonwealth Fund and conducted by three professorial experts in the fields of microscopical anatomy, biology, physiology and gynecology. The epithelial cytology of the normal human female reproductive tract is extensively examined, and its changes intensively studied in relation to the menstrual cycle. The results are embodied not only in the text but also in a large, colored folding chart, and are amplified and presented in twenty-three full-page plates of drawings and colored photomicrographs. There is a foreword by Dr. Joseph C. Hinsey, dean and professor of anatomy at Cornell University Medical College. In their introduction the authors review the literature of the subject, especially the epochal work of Rock and Hertig in the classification of the menstrual cycle, which is recorded in a bibliography of ninety titles.

This volume represents a monumental piece of research of permanent value, for it goes far to clarify and complete knowledge in the field and subject with which it deals, and was made possible by the intelligently co-ordinated and directed skills of investigators, technicians, and clinicians working harmoniously in a common enterprise toward a common objective.

NOTICES

POSITIONS FOR CIVILIAN DOCTORS IN PANAMA

Permanent appointments, in the Civil Service, for physicians now exist in the Panama Canal Medical Service. Salaries range from $5599 to $7794, with free transportation to the Canal Zone provided for physicians, their families and household goods. Return transportation is furnished upon completion of a minimum of one year's service. In addition, doctors who receive appointments get two months' paid vacation (including time lost by illness) and reduced fares on Panama Canal passenger vessels.

Requirements for position paying $5599 to $6540 are: graduation from an approved medical school; license to practice medicine in a state; ability to pass a standard physical examination; and completion of one year of internship in a hospital approved by the American Medical Association.

Requirements for positions paying $6540 to $7794 are the same except that a minimum of three years of post-internship experience is required.

Physicians who are interested in a position as medical officer in the Panama Canal Zone should communicate with Chief of Office, The Panama Canal, Washington, D. C. Applications may also be submitted to the United States Civil Service Commission, Washington, D. C.

(*Notices concluded on page xi*)

The New England
Journal of Medicine

Copyright, 1948, by the Massachusetts Medical Society

Volume 239 DECEMBER 30, 1948 Number 27

EARLY NEUROSYPHILIS

ISRAEL KOPP, M.D.*

BOSTON

INVASION of the central nervous system occurs in nearly all patients during the early stages of syphilis, usually during the first year of the infection. Early neurosyphilis is essentially a leptomeningitis. It is most often asymptomatic. The knowledge of its presence is of great importance since more intensive therapy and careful observation are necessary for these patients.

Early asymptomatic neurosyphilis can be detected only by spinal-fluid examination. The percentage of abnormal spinal fluids depends upon the time and frequency of the examination, ranging from 9 per cent in primary syphilis to 16 and 48 per cent in early and late secondary syphilis.[1] The degree of spinal-fluid abnormality is also of importance, since Moore[2] has shown that with inadequate treatment parenchymatous neurosyphilis will develop in 70 to 80 per cent of patients in whom early examination revealed severe or so-called Group III changes.

Despite these facts, syphilis of the central nervous system has been looked upon by some as a late development of the disease. This attitude has been fostered by the failure to do spinal-fluid examinations in early syphilis, by the rather infrequent appearance of early symptomatic neurosyphilis (meningitis and thromboses) and by the late development of symptomatic parenchymatous neurosyphilis (tabes, paresis, optic atrophy and so forth).

The finding of a normal spinal fluid in early syphilis, of less than two years' duration, does not always indicate that neurosyphilis will not occur in the future. Neurosyphilis may develop despite what is commonly accepted as intensive and adequate therapy with mapharsen, bismuth or penicillin. For this reason it is essential that spinal-fluid examinations be repeated over a period of years before the patient can be given complete assurance that neurosyphilis will not develop. A normal spinal fluid four or five years after the primary lesion, whether therapy has been given or not, will, in nearly all cases, assure the patient against the possibility of future parenchymatous neurosyphilis.

The following case reports bring out some important facts regarding the development, treatment and course of early neurosyphilis.

TABLE 1. *Spinal-Fluid Findings in Case 1.*

DATE	WASSERMANN REACTION	CELL COUNT	GLOBULIN	TOTAL PROTEIN	GOLD-SOL CURVE	COMMENT
		per cu. mm.		*mg. per 100 cc.*		
1/10/44	Negative	5	Negative	—	Negative	Before treatment
3/ 2/44	+ (0.5 cc.)	—	Negative	—	Negative	Before treatment
9/16/44	Negative	0	Negative	25		After mapharsen and bismuth therapy
7/12/45	+ (0.1 cc.)	218 lymphocytes 5 polymorphonuclears	Positive		Negative	Neurorelapse
9/ 8/45	+ (0.1 cc.)	197 lymphocytes	Trace	59	4444321000	—
10/12/45	+ (0.25 cc.)	5 lymphocytes	Negative	28	0023300000	After malaria and penicillin therapy

CASE REPORTS

In the following case of early asymptomatic neurosyphilis with mild spinal-fluid abnormality the spinal fluid became normal after intensive mapharsen and bismuth therapy. A severe neurorelapse occurred ten months later.

Case 1. H. J. A., a 31-year-old man, developed a penile lesion in October, 1943. The blood Kahn reaction was positive on November 27 and December 6. He was given forty intravenous injections of mapharsen (0.060 gm. each) and

*Research fellow, Department of Psychiatry, Harvard Medical School; research associate, Department of Mental Health, Boston Psychopathic Hospital; assistant physician, Beth Israel Hospital; attending physician, Neuropsychiatric Service, Veterans Administration Hospital, West Roxbury, Massachusetts; formerly, chief, Neurosyphilis Section, Schick General Hospital, Clinton, Iowa.

sixteen intramuscular injections of bismuth subsalicylate (0.200 gm. each) from March 10 to September 16, 1944. The results of spinal-fluid examinations are presented in Table 1.

Neurologic examination on August 30, 1945, was negative. The blood Kahn and Wassermann reactions were positive.

The patient was inoculated with tertian malaria on September 12 and was allowed ten paroxysms until October 6, 1945. He was also given one hundred and twenty doses of 30,000 units of penicillin intramuscularly at 3-hour intervals from September 30 to October 16, 1945.

This case provides an excellent example of the importance of repeated spinal-fluid examinations in early syphilis. The spinal fluid three months after the primary lesion and prior to any chemotherapy was completely normal. Two months thereafter and again before therapy, nervous-system involvement had already occurred, as revealed by a positive spinal-fluid Wassermann reaction in 0.5 cc. The spinal fluid was again completely normal immediately after intensive chemotherapy with mapharsen and bismuth, only to relapse and reveal marked abnormalities ten months later. The high cell count — 223 per cubic millimeter, with 98 per cent lymphocytes — is indicative of a fairly severe meningeal reaction. Since the patient was free of symptoms and neurologic examination was negative, the neurorelapse would have been overlooked had not the spinal-fluid examination been repeated. This type of abnormal fluid is of considerable prognostic significance in the development of future parenchymatous neurosyphilis. Intensive therapy, occasionally reinforced by fever, is necessary if such an event is to be prevented. The finding of even slight spinal-fluid abnormalities in early asymptomatic neurosyphilis is of considerable importance and necessitates frequent clinical and spinal-fluid re-evaluations.

The findings after combined penicillin and malaria therapy revealed the usual marked reduction in cell count and protein. Spinal fluid and clinical re-evaluations were recommended at six-month intervals until the spinal fluid becomes normal and then yearly for three years. Additional therapy, preferably penicillin, will be necessary if clinical or spinal-fluid relapse occurs.

In the following case of asymptomatic neurosyphilis with Group III spinal fluid and marked meningeal reaction nine months after seropositive primary syphilis and immediately after completion of an intensive course of mapharsen and bismuth therapy, spinal-fluid improvement followed additional chemotherapy with mapharsen, bismuth and penicillin.

TABLE 2. *Spinal-Fluid Findings in Case 2.*

DATE	WASSERMANN REACTION	CELL COUNT	GLOBULIN	TOTAL PROTEIN	GOLD-SOL CURVE	COMMENT
		per cu. mm.		*mg. per 100 cc.*		
10/ 5/44	+		Negative	—	Negative	After bismuth and mapharsen therapy
11/28/44	+ (0.1 cc.)	795 lymphocytes 309 polymorphonuclears	Negative	40	0022210000	—
2/26/45	+ (0.1 cc.)	17 lymphocytes 1 polymorphonuclear	Negative	10	0132200000	After additional chemotherapy

CASE 2. H. A. A., a 22-year-old Negro, developed a penile lesion on February 9, 1944. *Treponema pallidum* was not found on three dark-field examinations. The blood Kahn reaction was positive. Forty intravenous injections of mapharsen (0.060 gm. each) and fifteen intramuscular injections of bismuth subsalicylate (0.200 gm. each) were given from March 20 to September 22. The blood Kahn and Wassermann reactions were positive after treatment. The spinal-fluid findings are presented in Table 2.

The patient was given a second course of thirty-one injections of mapharsen (0.060 gm. each) and eight injections of bismuth subsalicylate (0.200 gm. each) from December 4, 1944, to February 28, 1945, and sixty doses of 40,000 units of penicillin intramuscularly at 3-hour intervals from January 27 to February 6, 1945.

TABLE 3. *Spinal-Fluid Findings in Case 3.*

DATE	WASSERMANN REACTION	CELL COUNT	GLOBULIN	TOTAL PROTEIN	GOLD-SOL CURVE	COMMENT
				mg. per 100 cc.		
7/18/45	—	0	Trace	52.5	3222110000	Xanthochromic fluid; questionable Kahn reaction.
8/ 7/45	++++	—	Positive		5543210000	—
9/ 8/45	+ (0.1 cc.)	2 lymphocytes	Trace	78.0	5554432100	—
11/13/45	+ (0.25 cc.)	2 lymphocytes	Negative	43.0	5443210000	After malaria inoculation and penicillin
	? (0.1 cc.)	1 polymorphonuclear				

Central-nervous-system syphilis was detected shortly after intensive mapharsen and bismuth therapy for primary syphilis. The spinal-fluid abnormalities were severe (Group III). The high cell count indicated a marked meningeal reaction, but there were no symptoms of meningitis. Additional mapharsen, bismuth and penicillin therapy

resulted in a marked reduction of the cell count, but the spinal fluid remained abnormal. Though continued chemotherapy with trivalent arsenicals or penicillin often results in a normal spinal fluid in early neurosyphilis, malarial therapy was recommended. Repeated clinical and spinal-fluid evaluations are necessary for this patient, as recommended in Case 1.

In the following asymptomatic neurosyphilis with Group III spinal fluid ten months after seropositive primary syphilis followed treatment with penicillin, mapharsen and bismuth. Combined malaria and penicillin was then administered.

Case 3. F. R., a 32-year-old Negro, developed a penile lesion in September, 1944. The blood Kahn reaction was positive on September 7.

He was given 60 doses of 40,000 units of penicillin intramuscularly at 3-hour intervals from September 11 to September 18. Because healing of the penile lesion was slow, he was also given forty intravenous injections of mapharsen (0.060 gm. each) and 16 intramuscular injections of bismuth subsalicylate (0.200 gm. each) from November, 1944, to July, 1945. The spinal-fluid findings are shown in Table 3.

Neurologic examination on September 1 was normal.

The patient was inoculated with quartan malaria on September 25 and allowed ten paroxysms to November 10. Fever was also induced on four occasions by means of mixed typhoid vaccine intravenously. He was given one hundred and twenty doses of 30,000 units of penicillin intramuscularly at 3-hour intervals from October 28 to November 12.

Intensive chemotherapy, consisting of penicillin, mapharsen, and bismuth for primary seropositive syphilis, did not prevent the development of asymptomatic neurosyphilis with strong spinal-fluid abnormalities. Involvement of the nervous system was first detected ten months after the primary lesion had appeared and immediately after chemotherapy had been completed. Because of the strong abnormalities in the spinal fluid, malarial therapy combined with penicillin was given. This case reveals the importance of a spinal-fluid examination before the patient is discharged from treatment. Frequent clinical and spinal fluid re-evaluations are necessary, as recommended in Case 1.

In the following case there were marked spinal-fluid abnormalities (Group III) six months after penicillin treatment of secondary syphilis. The patient was also treated with combined penicillin and malaria.

Case 4. A. S. P., a 29-year-old man, admitted repeated exposures in February and March, 1945. Lesions of the anus, penis, gums and tongue were noted on May 8. There was some hoarseness, as well as patchy areas of alopecia involving the scalp and eyebrows. Dark-field examinations of scrapings of the perianal lesion on May 8 and 9 revealed *Treponema pallidum*. A serologic test on May 8 revealed 240 Kahn units.

The patient was given sixty doses of 40,000 units of penicillin intramuscularly at 3-hour intervals from May 9 to May 15. The blood titer had fallen to 40 Kahn units on November 3.

The spinal-fluid findings 6 months after the secondary lesions had appeared and penicillin treatment had been instituted are presented in Table 4.

Neurologic examination was negative on November 17. The patient was inoculated with tertian malaria on January 12, 1946, and allowed nine paroxysms to January 31. He was given one hundred and twenty injections of 30,000 units of penicillin intramuscularly at 3-hour intervals from January 17 to February 1. Spinal-fluid examination after therapy was refused.

Penicillin therapy for secondary syphilis did not prevent the development of asymptomatic neurosyphilis with a Group III spinal fluid. The persistence of positive serologic tests should cause one to suspect involvement of the central nervous system. The incidence of neurosyphilis following penicillin therapy of early syphilis is estimated as less than 2 per cent. Repeated courses of penicillin with or without mapharsen and bismuth might well have resulted in a normal spinal fluid since this was a case of early asymptomatic neurosyphilis. However, as long-continued therapy and observation were not possible, combined malaria and penicillin therapy were recommended. If it is among this group that the future paresis or tabes is most apt to develop, early malarial therapy should be of great benefit.

In the following case of asymptomatic neurosyphilis with progressively severe abnormalities in the spinal fluid despite intensive chemotherapy for secondary syphilis, a reversal of Group III spinal fluid to normal occurred after penicillin, malaria and typhoid vaccine fever.

Case 5. M. E. H., a 28-year-old Negro, developed a primary lesion in December, 1943. This was followed by a right inguinal adenitis and a maculopapular rash of the face and back. Dark-field examination of the penile lesion was negative. The blood Kahn and Wassermann reactions were positive in December, 1943, and January, 1944. Forty intravenous injections of mapharsen (0.060 gm. each) and fifteen intramuscular injections of bismuth subsalicylate (0.200 gm. each) were given from January 18 to August 31.

The blood Kahn reaction became negative after treatment, remaining so until February, 1945, and then relapsing to positive. The results of the spinal-fluid examinations are shown in Table 5.

Table 4. *Spinal-Fluid Findings in Case 4.*

Date	Wassermann Reaction	Cell Count	Globulin	Total Protein	Gold-Sol Curve
		per cu. mm.		*mg. per 100 cc.*	
11/ 5/45	+ (0.1 cc.)	45	++	—	5544332100
11/20/45	+ (0.1 cc.)	156 lymphocytes	Slight trace	57	5554321000

The patient was given eighty doses of 50,000 units intramuscularly of penicillin at 3-hour intervals from March 21 to March 31. He was inoculated with quartan malaria on May 24, and allowed eight paroxysms until July 26. Fever was also induced on seven occasions by means of mixed typhoid vaccine intravenously.

One year after a primary lesion and about three months after completion of intensive chemotherapy, the spinal fluid revealed an increase in cells, which was indicative of central-nervous-system involvement. Two months thereafter the spinal-fluid developed in February, 1944. A diagnosis of lymphogranuloma inguinale was made. He was given sulfonamide therapy. The lymph nodes became less tender but remained enlarged for 3 or 4 months. A serologic test was positive in January and February, 1945. The results of spinal-fluid examination are presented in Table 6.

He was given fifteen intravenous injections of mapharsen (0.060 gm. each) and five intramuscular injections of bismuth subsalicylate (0.200 gm. each) from February 26 to April 13. The spinal fluid reverted to normal in 5 months.

Neurologic examination on June 30 was negative, as was a Frei test on July 7. The blood Kahn and Wassermann reactions were positive.

TABLE 5. *Spinal-Fluid Findings in Case 5.*

DATE	WASSERMANN REACTION	CELL COUNT	GLOBULIN	TOTAL PROTEIN	GOLD-SOL CURVE	COMMENT
		per cu. mm.		*mg. per 100 cc.*		
12/ 4/44	Not determined	32	—	—	Negative	—
2/ 9/45	—	73	+	—	5555421000	Kahn reaction positive
2/18/45	+ (0.25 cc.)	23 lymphocytes	+	120	5555321000	—
	? (0.1 cc.)	9 polymorphonuclears				
5/ 1/45	? (1.0 cc.)	15 lymphocytes	+	96	5543310000	After penicillin
8/27/45	Negative (1.0 cc.)	5 lymphocytes	Trace	45	1100000000	After malaria inoculation

abnormalities were severe (Group III). The fluid showed some improvement after the administration of penicillin and became practically normal after fever therapy.

It is possible that the spinal fluid would eventually have become normal as a result of penicillin therapy alone. Moore[3] states that the speed and extent of disappearance of all spinal-fluid abnormalities following penicillin depends upon the degree of these abnormalities before treatment and the duration of the syphilitic infection. In a series of 91 patients with asymptomatic neurosyphilis, 48 of less than four years' duration, observed on an average for about nine months, spinal-fluid normality once obtained seemed to be sustained. Serologic relapse like that in Case 5, which should always alert one to the possible presence of early neurosyphilis, demands a spinal-fluid examination.

In the following case of early asymptomatic neurosyphilis with marked spinal-fluid abnormalities, the spinal fluid became normal after a moderate amount of mapharsen and bismuth therapy.

CASE 6. J. L. R., a 24-year-old man, had negative serologic tests in December, 1942. A penile lesion appeared 7 to 10 days after exposure in December, 1943. Dark-field examinations were negative. Left inguinal adenopathy

From July 12 to July 19 the patient was given sixty injections of 40,000 units of penicillin intramuscularly at 3-hour intervals.

The neurosyphilis in this case was asymptomatic and evidently early. The penile lesion in December, 1943, was probably a chancre and not lymphogranuloma inguinale, since a Frei test two and a half years later was negative. A moderate amount of mapharsen and bismuth therapy had rapidly reversed a Group III spinal fluid to normal. This is not uncommon in early asymptomatic neurosyphilis. However, repeated spinal-fluid and clinical re-evaluation for four years at least is necessary since relapse is not uncommon with this degree of abnormality.

In the following case of early meningovascular neurosyphilis with right cerebral thrombosis spinal-fluid abnormalities persisted after two courses of penicillin; malaria therapy was instituted.

CASE 7. H. J. B., a 27-year-old man, had a negative serologic test on December 15, 1943. On May 23, 1945, a central weakness of the left facial muscles developed, accompanied by a left hemiparesis. The spinal-fluid findings are shown in Table 7.

The Wassermann and Kahn reactions of the blood were positive on June 8. From June 23 to July 3 eighty doses of

TABLE 6. *Spinal-Fluid Findings in Case 6.*

DATE	WASSERMANN REACTION	CELL COUNT	GLOBULIN	TOTAL PROTEIN	GOLD-SOL CURVE	COMMENT
		per cu. mm.		*mg. per 100 cc.*		
2/15/45	++++	108 lymphocytes 12 polymorphonuclears	—	53.5	5554420000	—
2/28/45	++++	102 lymphocytes 11 polymorphonuclears	—	65.5	5554442000	—
7/ 4/45	Negative (1.0 cc.)	4 lymphocytes	Negative	36.0	1110000000	After bismuth and mapharsen

50,000 units of penicillin were administered intramuscularly at 3-hour intervals.

On August 8 neurologic examination revealed brisk and equal reflexes and a left Babinski sign. The serologic tests were again positive. The subsequent spinal-fluid findings are presented in Table 7.

The patient was given a second course of penicillin, consisting of one hundred and twenty doses of 30,000 units intramuscularly at 3-hour intervals from September 7 to 22. Since the protein and cell count remained elevated after completion of penicillin therapy, he was inoculated with tertian malaria and allowed eleven paroxysms.

Early symptomatic neurosyphilis is not common. The patient gave no history of primary or secondary syphilis. The first sign of neurosyphilis was weakness of the left side of the face and left side of the body. This was indicative of a vascular lesion, but pure syphilitic arteritis rarely occurs without an associated meningitis or meningoencephalitis. Though syphilis had been suspected as the cause after the finding of 284 cells per cubic millimeter in the spinal fluid, the Wassermann reaction of the spinal fluid and blood had not been determined. Strong spinal-fluid abnormalities and a positive serologic test were found two weeks thereafter. Spinal-fluid abnormalities were still present after two courses of penicillin, and it was considered best to administer malaria therapy. Clinical and spinal-fluid re-evaluations, as in Case 1, were recommended.

In the following case of early meningovascular neurosyphilis with Jacksonian attacks moderately severe spinal-fluid abnormalities rapidly returned to normal after 2,400,000 units of penicillin had been administered.

Table 7. *Spinal-Fluid Findings in Case 7.*

Date	Wassermann Reaction	Cell Count	Globulin	Total Protein	Gold-Sol Curve	Comment
		per cu. mm.		*mg. per 100 cc.*		
5/23/45	—	284	Negative	—	—	—
6/ 8/45	Positive	99 lymphocytes	++++	23	4433200000	—
8/11/45	+ (0.25 cc.)	25 lymphocytes	Trace	108	Negative	After penicillin
9/24/45	+ (0.5 cc.) ? (0.25 cc.)	27 lymphocytes	Negative	85	0011221000	After additional penicillin
11/ 6/45	+ (0.5 cc.) ? (0.1 cc.)	5 lymphocytes	Negative	90	1100000000	After malaria therapy

Case 8. R. E. R., a 27-year-old man, had a negative serologic test in August, 1942. Because of a gonorrheal infection in July, 1945, he was given four doses of 50,000 units of penicillin intramuscularly. He was again given some penicillin therapy, the exact amount not known, in September because of tonsillitis.

On October 3, he experienced a grand mal seizure with involvement of the right side of the face and right upper extremity. On October 5, 8 and 9 similar episodes without loss of consciousness occurred. During this time he complained of left frontal headaches. Central weakness of the right facial muscles and slurring of speech were observed on October 13.

The quantitative titer of the blood on October 13 and 15 was 10 Kahn units. X-ray study of the skull was negative. The spinal-fluid pressure and dynamics were normal. A sugar tolerance test was normal. The spinal-fluid findings are presented in Table 8.

From October 15 to 22 sixty doses of 40,000 units of penicillin were administered intramuscularly at 3-hour intervals. Neurologic examination on October 30 revealed central weakness of the right facial muscles, and the reflexes of the right upper extremity were more active than those on the left.

The serologic titer on November 2 was 40 Kahn units; the blood Wassermann reaction was positive.

From January 9 to 16, 1946, the patient was given a second course of penicillin consisting of sixty doses of 40,000 units intramuscularly at 3-hour intervals.

The serologic titer was 10 Kahn units and the blood Wassermann reaction was negative on January 17.

Table 8. *Spinal-Fluid Findings in Case 8.*

Date	Wassermann Reaction	Cell Count	Globulin	Total Protein	Gold-Sol Curve	Comment
		per cu. mm.		*mg. per 100 cc.*		
10/13/45	—	63 lymphocytes 1 polymorphonuclear	—	45	—	Kahn test positive
10/27/45	—	22 lymphocytes	—	32	—	After penicillin
12/ 4/45	Negative (1.0 cc.)	3 lympocytes	Negative	40	Negative	Initial spinal-fluid pressure was equivalent to 145 mm. of water; dynamics normal.

A convulsive episode may be the first indication of neurosyphilis, early or late. This is due to a thrombosis of a cortical vessel that occasionally occurs in the leptomeningitis of neurosyphilis. The moderately severe spinal-fluid abnormalities rapidly reverted to normal after 2,400,000 units of penicillin had been administered. The patient will require clinical and spinal-fluid re-evaluations for at least three years. The convulsive episodes disappear in most cases with adequate antisyphilitic therapy. If they recur, anticonvulsants should be given.

In the following case of syphilitic meningitis with cerebral thrombosis in early syphilis the patient suffered a neurorelapse.

CASE 9. W. R. C., a 21-year-old man, developed a penile lesion in December, 1942. He received three intravenous treatments. A serologic test on February 12 and March 26, 1943, was positive. The spinal-fluid findings are presented in Table 9.

He was given thirty-nine injections of mapharsen (0.060 gm. each) and seventeen of bismuth subsalicylate (0.200 gm. each) from May to December.

From December, 1944, on he experienced frontal headaches of 2 or 3 hours' duration. Dizzy spells occurred in May, 1945. Numbness of the right forearm and the fourth and fifth fingers over 1 week's time was present in August. He was aphasic from September 1 to 8. There was also weakness of the right upper extremity and numbness of the ulnar portion of the forearm.

A serologic test on September 7 revealed 40 Kahn units. Physical examination showed dysarthria, loss of the finer movements of the right hand and absent right abdominal reflexes.

The serologic titer on October 18 was 40 Kahn units; the blood Wassermann reaction was positive.

He was inoculated with tertian malaria on November 17 and allowed eleven paroxysms until December 9. He was also given one hundred and twenty doses of 30,000 units of penicillin intramuscularly at 3-hour intervals from November 22 to December 7.

TABLE 9. *Spinal-Fluid Findings in Case 9.*

DATE	WASSERMANN REACTION	CELL COUNT	GLOBULIN	TOTAL PROTEIN	GOLD-SOL CURVE	COMMENT
		per cu. mm.		*mg. per 100 cc.*		
5/ 8/43	Negative (0.5 cc.)	110	Negative	—	—	—
12/ 6/43	Negative	2	Negative	—	Negative	After bismuth and mapharsen
10/27/45	+ (0.25 cc.) ? (0.1 cc.)	172 lymphocytes	Trace	76	4443331000	—
12/11/45	+ (0.25 cc.) ? (0.1 cc.)	9 lymphocytes	Trace	46	5443210000	After penicillin and malaria

This patient's spinal fluid revealed an increase in cell count five months after the appearance of a primary lesion. The spinal fluid was normal immediately after the completion of seven months of intensive mapharsen and bismuth therapy. One year later, progressively severe symptoms referable to the central nervous system developed. Neurorelapse with spinal-fluid abnormalities, Group III in type, were found twenty-two months after a normal spinal-fluid had been obtained and three years after the primary lesion.

The sequence of events in this patient again emphasizes the fact that one cannot rely on a single normal spinal-fluid specimen in early neurosyphilis, especially an examination performed shortly after the completion of chemotherapy. In addition, the necessity of adequate therapy for syphilitic meningitis has been stressed by various observers, since two thirds of inadequately treated patients have developed parenchymatous and late meningovascular neurosyphilis.[4] Since the patient's syphilis was of three years' duration, malaria therapy was given without hesitation.

DISCUSSION

The cases reported above are examples of early asymptomatic and symptomatic neurosyphilis. Of 154 cases of asymptomatic neurosyphilis from November, 1944, to February, 1946, 25 (15 per cent) were of less than two years' duration when the patients were first seen. Spinal-fluid abnormalities of varying degree were found from the secondary stage of syphilis on. These abnormalities may clear with chemotherapy, mapharsen, bismuth or penicillin, but occasionally relapse occurs despite intensive therapy.

These cases support the advice that treatment for early syphilis cannot be considered satisfactory unless a spinal-fluid examination is done before the patient is discharged. If the spinal fluid is normal, adequate follow-up study requires that it should be normal again at least four years after the primary lesion. If spinal-fluid abnormalities are present during the first two years of the infection, additional chemotherapy (formerly trivalent arsenicals and bismuth, now penicillin) is necessary, since early neurosyphilis will respond most often to chemotherapy alone. If marked improvement or a normal spinal fluid does not result within a year, fever therapy is given. However, if the infection is of more than two years' duration when the patient is first seen and significant spinal-fluid abnormalities are present, fever therapy should be administered immediately, combined now with penicillin. Further experience will be necessary before it can be determined whether penicillin alone will be adequate in these cases, as has been reported by some observers.[5]

The majority of the patients with early asymptomatic neurosyphilis included in this study had already received chemotherapy consisting of trivalent arsenicals and bismuth. A few had received penicillin. In many cases the treatment was considered adequate according to present standards. With the introduction of penicillin, it is now necessary to determine new methods for the treatment of neurosyphilis. It is already apparent that the incidence of neurosyphilis has been reduced considerably as a result of the treatment of early

syphilis with penicillin. Used alone, the drug has proved very effective in the treatment of syphilitic meningitis, asymptomatic and meningovascular neurosyphilis and, in the opinion of some observers, in parenchymatous neurosyphilis.

It is also evident from the cases reported above that malaria therapy was administered quite early for the treatment of neurosyphilis. Undoubtedly the spinal-fluid abnormalities in some cases would have responded to additional chemotherapy alone. Since it is especially among the patients with severe spinal-fluid abnormalities that future parenchymatous neurosyphilis may develop, and since circumstances prevented long-continued chemotherapy and observation in this group, malaria therapy was given early. Clinical and spinal-fluid evaluations of these patients over the years should be of considerable interest in demonstrating the preventive effect of combined malaria and penicillin therapy of early neurosyphilis upon the development of late parenchymatous disorders.

Prior to the introduction of penicillin, Moore[6] had expressed the opinion that fever therapy in asymptomatic neurosyphilis is seldom necessary except in patients with Group III spinal fluids and those of other groups in whom at least eighteen months of other forms of treatment had failed to effect serologic reversal. Malaria was not recommended by him if the infection was recent until the patient had had at least six months' treatment with the arsphenamines and heavy metal given for the treponemicidal effect. The latter was advised because of the great probability of infectious mucocutaneous relapse. It is possible that this objection can now be overcome by the concurrent use of penicillin, with its pronounced treponemicidal effect, and malaria.

Summary

Invasion of the central nervous system in syphilis is early, occurring in nearly all patients, usually within the first year of the infection.

Early neurosyphilis is most often asymptomatic but occasionally is symptomatic. When asymptomatic, it can be detected only by spinal-fluid examination.

Neurosyphilis may develop despite the administration of what is commonly accepted as adequate chemotherapy for early syphilis.

Complete reliance cannot be placed on the finding of a single normal spinal-fluid specimen in early syphilis before or immediately after therapy.

A negative spinal-fluid examination four years or more after the primary lesion, regardless of whether therapy has been given, is good assurance against the future development of meningovascular or parenchymatous neurosyphilis.

The treatment of early syphilis with penicillin has reduced considerably the incidence of early neurosyphilis. Penicillin alone is of great benefit in the therapy of neurosyphilis of the asymptomatic, meningovascular and meningitic types. Further experience is necessary to determine its value as the sole treatment for parenchymatous (general paresis, tabes dorsalis, optic atrophy and so forth) neurosyphilis.

74 Fenwood Road

References

1. Mills, H. Zurhelle, E., and Krechel, J. Cited by Merritt, H. H., Adams, R. D., and Solomon, H. C. *Neurosyphilis*. 443 pp. New York: Oxford University Press 1946. P. 7.
2. Moore, J. E. *Modern Treatment of Syphilis*. Second edition. 712 pp. Springfield, Ill.: Charles C Thomas, 1947. Pp. 364 and 365.
3. *Idem. Penicillin in Syphilis*. 319 pp. Springfield, Ill.: Charles C Thomas, 1946. Pp. 239 and 240.
4. Moore.[2] P. 365.
5. Dattner, B. Neurosyphilis and latest methods of treatment. *M. Clin. North America* **32**:707-719, 1948.
6. Moore.[2] P. 418.

HOSPITAL AND HEALTH-CENTER FACILITIES IN MASSACHUSETTS

The Massachusetts State Plan for the Administration of Public Law 725 (Hospital Survey and Construction Act)

VLADO A. GETTING, M.D., DR.P.H.,* A. DANIEL RUBENSTEIN, M.D.,† AND CLAIRE F. RYDER, M.D.‡

BOSTON

THE acute shortage of hospital beds experienced everywhere in the country during the past few years resulted in 1946 in the enactment of Public Law 725 by the Seventy-Ninth Congress. This act, the Hospital Survey and Construction Act, previously known as Senate Bill 191, or the Hill–Burton Bill, was the first and only bill to be endorsed in Congressional hearings by the American Public Health Association, the American Hospital Association and the American Medical Association. The purpose of the Act is to enable communities throughout the nation to construct hospitals and health-center facilities under a federal grants-in-aid program for a period of five years beginning July 1, 1947. Such facilities are to be provided on the basis of need according to plans developed by each state. The federal Government is contributing a third of the cost of constructing and equipping hospitals and health centers, and the remaining two thirds is derived from sources within the state.

Of the $75,000,000 authorized by Congress for hospital construction during the first year of the program, approximately $1,600,000 has been allotted to Massachusetts. The amount of the grant to Massachusetts for the five-year period of the program totals approximately $8,000,000. Since each dollar of federal grants must be matched by two dollars from state or local sources, the total expenditure under this program in Massachusetts amounts to $24,000,000. State, county, municipal and private nonprofit hospitals may be assisted if individual projects are approved by the state operating agency (usually the health department) and the United States Public Health Service, and provided that the project is in accord with the plan[1] formulated by the state agency to meet the needs for additional facilities. The Massachusetts State Plan was approved by the Surgeon General of the United States Public Health Service on December 2, 1947. The state agency in Massachusetts directly responsible for the administration of Public Law 725 is the Department of Public Health. For the administration of this Act, a bureau of hospital survey and construction has been created, and an advisory council to the state agency has been appointed.

*Commissioner, Massachusetts Department of Public Health.
†Director of Hospital Survey and Construction.
‡Epidemiologist, Hospital Survey and Construction.

In accordance with the regulations promulgated by the United States Public Health Service regarding Public Law 725, the Commonwealth of Massachusetts has been divided into three types of hospital service areas — namely, base, intermediate and rural.

A base area is defined as one that, irrespective of population, contains a teaching hospital of a medical school, or one that has a total population of at least 100,000 and contains or will contain a general hospital of 200 beds or more providing internships and at least two or more residencies. An intermediate area has at least 25,000 persons and contains or will contain a general hospital of 100 beds or more. A rural area has a population under 25,000.

For the purposes of the Act, the term "hospital" includes public-health centers, general, tuberculosis, mental-disease and chronic-disease hospitals, and related facilities such as laboratories, outpatient departments, nurses' homes and schools and all service facilities operated in connection with such institutions. Federal hospitals and institutions providing primarily domiciliary care are not included in the above definitions.

Bed allowance for general hospitals is based upon the state's population density. In Massachusetts, with more than 12 persons per square mile, the maximum state allowance for general hospital beds is 4.5 per thousand population. Standards for area ratios also depend on population density. In Massachusetts, area ratio standards are as follows: base areas, 4.5 beds per thousand population; intermediate areas, 4 beds per thousand population; and rural areas, 2.5 beds per thousand population.

The differences in the number of beds allowable under the state and area ratios may be totaled and thus constitute a pool of general-hospital beds. Pool beds may be distributed throughout the state at the discretion of the state agency according to the needs of various areas. The number of beds required to provide adequate hospital services for the care of tuberculosis patients amounts to two and a half times the average annual deaths from tuberculosis, for mental patients, 5 beds per thousand population, and for patients with chronic diseases, 2 beds per thousand population. The total number of public-health centers allowed shall not exceed 1 for 30,000 persons.

In the development of the hospital-construction program, consideration must be given to each of the five categories of facilities: general, tuberculosis and mental and chronic-disease hospitals and public-health centers. New hospitals and additions to existing hospitals have priority over replacements, with the exception of hospitals that constitute a public hazard and should be replaced. It is the intent of the law to provide facilities in areas of greatest need. Special attention must be given to projects in rural areas or in communities of low economic resources.

Existing Facilities

In the development of the state plan for the administration of the Act, a survey of existing hospital and health-center facilities in Massachusetts has been completed. There are in the Commonwealth a total of 219 hospitals with a normal bed capacity of 44,044 beds. Of these institutions, 147 are general hospitals with 16,968 beds, and 24 allied special hospitals with 2210 beds (Table 1).

It is noteworthy that of the 147 general hospitals, 92 have 100 beds or less, 44 have 100 to 249 beds, and only 11 have 250 beds or more (Table 2).

There are 20 tuberculosis institutions with a total bed capacity of 3299 (Table 1). Of these,

Table 1. *Distribution of Hospitals by Type.*

Type	Total Number		
	Hospitals	Beds*	
General	147	16,968	
Maternity	6	379	
Contagious	6	564	
Other special	12	1,267	
Subtotals of general and allied special	171		19,178
Tuberculosis	20		3,299
Nervous and mental	24		21,050
Chronic and convalescent	4		517
Grand totals	219		44,044

*The figures referring to number of beds indicate the normal bed capacity — that is, the number of beds for which the hospital was built. In many instances because of overcrowding, this figure is smaller than the actual number of beds in use for inpatient care (complement).

4 are nongovernmental, nonprofit associations, and the remaining 16 are governmental hospitals. Of the latter, 12 are owned by cities or counties and provide nearly 2000 beds, primarily for the care of the patients with local settlements, and 2 are state institutions having a bed capacity of about 600 beds. In addition, there are 2 state hospitals caring for patients with extrapulmonary tuberculosis and tuberculosis in children. If tuberculosis units in general or board of health hospitals are included, the total number of existing beds for the care of tuberculosis is 3611.

In Massachusetts there are 24 mental hospitals with a normal bed capacity of 21,050 (Table 1). Of these, 12 institutions with a total of 604 beds are nongovernmental, and the remaining 12 with 20,446 beds are state owned.

Existing facilities for the care of patients with long-term illness are entirely inadequate in the Commonwealth as they are everywhere else in the country. There are now only 1100 beds for patients with chronic diseases in Massachusetts hospitals. How this shortage is to be overcome is a matter of debate. In Springfield, one hospital has set aside a complete ward for such patients. Although this ward was set up more than ten years ago, certain patients admitted at the time of its inception are still occupying beds in this institution. The problem is even more acute for certain categories of patients, such as those with terminal cancer. Ordinarily, these patients are not accepted

Table 2. *Distribution of General Hospitals by Size.*

Size	Total Number	
	Hospitals	Beds*
Less than 25 beds	23	436
25–49 beds	32	1,113
50–99 beds	37	2,460
100–249 beds	44	7,178
250–499 beds	8	2,597
More than 500 beds	3	3,184
Totals	147	16,968

*The figures referring to number of beds indicate the normal bed capacity — that is, number of beds for which the hospital was built. In many instances because of overcrowding, this figure is smaller than the actual number of beds in use for inpatient care (complement).

for admission into general hospitals for indefinite or prolonged periods of stay. Nursing homes and convalescent homes are often too inadequately staffed to care for them. In summary, there are practically no facilities for the patient requiring terminal care.

Although each of the 351 municipalities is required by law to carry out certain governmental functions in the field of public health, as defined by Public Law 725, there are but 11 health centers in the Commonwealth. Of these, 10 are in Boston proper. The other is the public-health center in Ayer, maintained by the Nashoba Health Unit, a union of several towns in the north central section.

Hospital Service Areas

In keeping with requirements of Public Law 725, all cities and towns in Massachusetts, singly or in groups, are designated as the service areas of existing or proposed general hospitals. Accordingly, the Commonwealth was divided into 70 general-hospital service areas. Each of these areas contains at least one general hospital, with the exception of one area (Athol) where a new hospital facility has been proposed. Determination of the service area was based primarily on available data regarding the flow of patients into the hospital. Other factors taken into consideration were location of trading centers and lines of communication. Subsequently, each hospital service area was clas-

sified as base, intermediate or rural (the prerequisites of these area types were described above). Of the 70 hospital service areas in Massachusetts, 4 are base, 43 intermediate, and 23 rural.

In addition, the state plan provides a method whereby each hospital service area will be co-ordinated with all others so that a uniform pattern of hospital care shall be formulated for the entire Commonwealth. Theoretically, the base areas should offer consultation and diagnostic services to the intermediate areas, which, in turn, offer similar service to rural areas. To allow for this exchange of facilities, Massachusetts was divided into 6 regions of which 3 are composed of intermediate and rural areas, and the other 3 contain in addition base areas. The former are the Beverly-Salem, Barnstable and Pittsfield regions, and the latter, the Boston, Worcester and Springfield regions (Fig. 1).

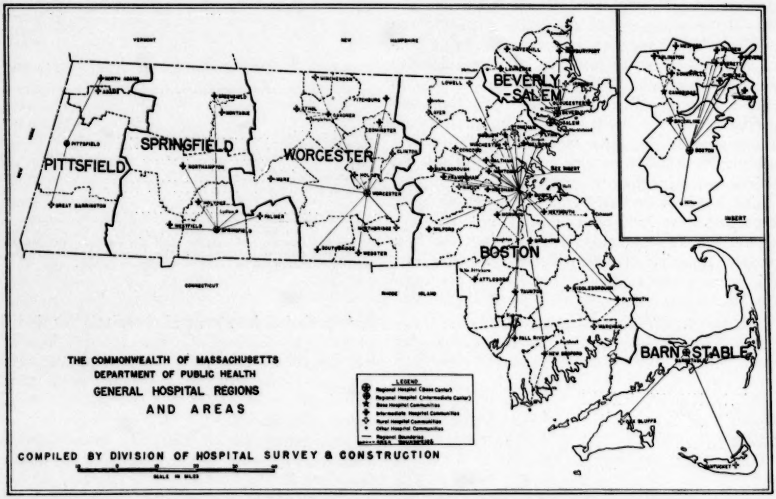


FIGURE 1. *Hospital Service Areas in Massachusetts.*

DETERMINATION OF NEEDS FOR HOSPITALS AND HEALTH CENTERS

The number of beds apportioned to each general hospital service area is determined according to the formula established by law as mentioned above. Of 3944 beds added by area ratio in Massachusetts, nearly all (3285 beds) went to intermediate areas and only 454 and 205 to base and rural areas respectively. Pool beds may be allocated to areas in which the number assigned by area ratio is insufficient for the needs of the jurisdiction. Pool beds were assigned in proportion to high occupancy rates, excessive bed-death ratios and special problems such as seasonal increases in population. Of the 1661 pool beds, the greatest number was allocated to base areas (1011 beds), intermediate areas being allotted 440 and rural areas 210 beds (Table 3).

The number of existing and needed beds according to the several categories is as follows: there are 18,224 general-hospital beds, whereas 23,829 beds are needed according to Public Law 725, making a deficit of 5605 beds. For the care of tuberculosis, Massachusetts has in existence 3604 beds; 4408 beds are needed. Therefore, 804 additional beds must be provided. For patients with mental disease, there are 21,102 beds; 1738 additional beds are needed, since the total beds allowed are 22,840. Finally, for chronic-disease hospital facilities, there are only 1100 beds in existence; 9136 are needed, and therefore, a deficit of 8036 exists. The figures of need met in these four categories of facilities are 76 per cent for general-hospital beds, 82 per cent for tuberculosis, 92 per cent for mental-disease and 12 per cent for chronic-disease beds (Fig. 2).

The state plan must also give consideration to the need for health centers in Massachusetts. For the Commonwealth as a whole, 31 public-health

centers are being proposed. For the most part, these centers have been allocated to the larger cities and towns with a population of 30,000 or more. It should be noted, in accordance with the ratio of 1 health center for each 30,000 persons, that many of the larger cities could plan for more than one health center provided that matching local funds were available. In addition, a health center has been proposed in Amherst for the Connecticut Valley State Health District and another for Barnstable County.

A recent report issued by the Special Commission to Study and Investigate Certain Public Health Matters[2] will suggest a plan to provide full-time health service for the entire Commonwealth. The findings of the Recess Commission will be given full consideration by the state agency and the advisory council in future planning of adequate health-center facilities, including physical plant and personnel.

Priority Schedules

To facilitate the equitable distribution of federal funds available for the construction of general hospitals, a system of priorities has been developed. This system gives full consideration to the provisions required in Public Law 725 and the federal regulations — namely, the relative need for beds in an area, rural character of the hospital service area and the financial rating.

Percentage of need met is determined by division of the total number of existing acceptable beds in each area by the total number of beds needed in the area, this figure being multiplied by 100 for the percentage. Rural character is established by the Act as any area with a population less than 25,000.

In 1941, Dr. Morris B. Lambie[3] conducted a study of the municipal finances of the 351 cities and towns in the Commonwealth at the Harvard Graduate School of Public Administration. His comparative rating of these municipalities was based on three-year averages of three factors: tax rates, assessed per capita valuation, and direct tax per capita. According to these criteria, the municipalities were classified into eleven categories. Communities in the first grouping have relatively greater financial resources than communities low in Dr. Lambie's rating.

The primary consideration in developing the priority schedule was the percentage by which the existing acceptable hospital beds within an area met the total needs of that area. From the percentage of need met, additional deductions were made for rural areas and those of low financial rating. The final figure determined the standing in the priority scheme (Table 4).

Table 3. *Relation of Population to Existing and Proposed General-Hospital Beds.*

Area Type	Existing Beds		Beds Added by Area Ratio	Beds Added from Pool	Total Beds Needed		Population	
	No.	Percentage			No.	Percentage	No.*	Percentage
Base	9,161	50.3	454	1,011	10,626	44.6	1,612	35.3
Intermediate	8,026	44.0	3,285	440	11,751	49.3	2,605	57.0
Rural	1,037	5.7	205	210	1,452	6.1	350	7.7
Totals	18,224		3,944	1,661	23,829		4,567	

*In thousands.

The priority scheme for chronic-hospital projects has been computed in the same manner as for general hospitals, and is based primarily on the percentage of need met. Metropolitan areas of greatest population density will stand highest in the scheme. With respect to general hospitals it became apparent that strict application of the federal formula favored rural and intermediate areas rather than base areas. It was believed that construction of chronic-hospital units in metropolitan areas would compensate in part for the low standing in the priority schedule of the base areas. It will therefore be possible to allocate federal funds for chronic-hospital projects in such areas as Boston, Worcester, Springfield and Pittsfield.

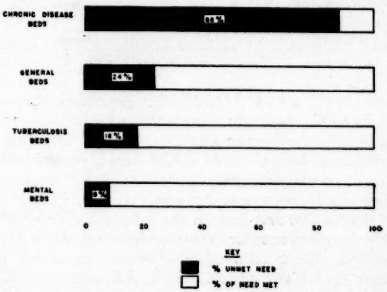


Figure 2. *Need for Additional Hospital Beds in Massachusetts.*

The need for public-health centers in the Commonwealth is so great that no attempt has been made to establish a priority scheme for this cate-

gory. Applications will be considered as they are submitted. It is expected that at least some of the larger communities will take advantage of federal assistance for the construction of health centers.

As indicated above, the need for tuberculosis and mental beds is relatively less than that for beds in chronic and general hospitals. It has been determined that at least for the first two years of the program, federal assistance will be devoted to the construction of general and chronic hospitals and public-health centers.

The federal funds provisionally allotted for these three categories during the fiscal years 1948 and 1949 are $1,177,128 for general hospitals, $1,119,707 for chronic-disease hospitals, and $574,209 for public-health centers. The total amount of federal funds is $2,871,044, representing an allotment of $3,190,050, less a 10 per cent contingency fund for rising prices.

During the first year of the program (1947-1948) five applications for new construction were approved. The total number of beds to be added by these projects is approximately 300, of which 225 are of the general-hospital and 75 of the chronic-hospital category.

TABLE 4. *Rank of General-Hospital Areas in First Two Priority Groups (1947–1948).*

PRIORITY	AREA NO.	AREA NAME
A-1	R-17	Athol
A-2	I-18	Needham
A-3	I-17	Medford
A-4	R-12	Northbridge
A-5	I-31	Woburn
A-6	I-32	Milford
A-7	R-9	Ipswich
B-1	R-16	Webster
B-2	R-6	Concord
B-3	I-20	Revere
B-4	I-43	Marlboro
B-5	I-21	Somerville
B-6	I-12	Arlington
B-7	I-11	Weymouth
B-8	I-15	Everett
B-9	R-13	Palmer
B-10	I-2	Barnstable
B-11	I-9	Norwood
B-12	I-7	Brockton
B-13	I-5	Plymouth
B-14	I-6	Taunton
B-15	I-28	Melrose

DISCUSSION

From Table 3 it is apparent that 50 per cent of existing hospital beds are in base areas that have 35 per cent of the population, whereas 44 per cent of the beds are in intermediate areas with 57 per cent of the population. The figures of the rural areas are more nearly equal — namely, 5.7 per cent of the beds and 7.7 per cent of the population.

After application of the federal formulas developed under Public Law 725, the discrepancies between the percentage of population and the percentage of total beds needed in base and intermediate areas are diminished but not to a marked degree. In other words, the general pattern of the distribution of general-hospital beds in suburban and rural areas has not been altered to a marked extent. It was believed that general hospitals in Massachusetts have grown in accordance with the need of the population for this type of medical facility. It was the policy of the state agency in setting up the plan not to interfere with this natural development.

It is expected that the priority scheme for the general-hospital category will be altered for the second year of the program to take into account obsolescent and substandard facilities. Several of the general hospitals in Massachusetts were built at the turn of the century and are obsolete according to modern specifications. Many are frame buildings or of substandard construction in other respects. It is apparent, therefore, that many beds will be declared noncomputable as far as this plan is concerned. This will alter considerably the priority standing of many areas that are now low in the schedule to a much more favorable position.

Funds allocated by the federal Government for this program are inadequate to fulfill the entire need within the Commonwealth. The state plan indicates an over-all lack of 16,183 beds in all categories. A conservative estimate for the cost of building these beds is roughly $190,000,000, exclusive of public-health centers. It is apparent, therefore, that the total of $24,000,000 that would be spent under this program is by no means adequate to construct all necessary facilities. The cost of construction has risen to such a degree that without federal assistance many projects that have been planned will not be undertaken. All of this may be taken as evidence that Public Law 725 is meeting a great need in the Commonwealth.

SUMMARY

A survey of existing hospital facilities revealed that there are 219 hospitals in Massachusetts with a normal bed capacity of 44,044.

In accordance with the provisions of Public Law 725, the Commonwealth was divided into 70 general hospital service areas of which 4 are base, 43 intermediate and 23 rural. In addition, to provide an integrated hospital system, 6 regions were formed, composed of the service areas mentioned above.

By application of the formulas contained in the Act, it was found that there is a deficit of 16,183 beds, of which 5605 are general, 804 tuberculosis, 1738 mental-disease and 8036 chronic-disease beds.

A priority schedule based primarily upon need for additional beds has been established for general and chronic hospitals.

REFERENCES

1. Massachusetts State Plan for the Administration of Public Law 725 (Hospital Survey and Construction Act)
2. *Report of the Special Commission to Study and Investigate Certain Public Health Matters* (Chapter 73 of the *Resolves* of 1947). December 3, 1947. Commonwealth of Massachusetts.
3. Lambie, M. B. *Experiments in Methods of Municipal Analysis.* 306 pp. Cambridge, Mass.: Bureau for Research in Municipal Government, Harvard School of Public Administration, 1941. Pp. 101-104

PNEUMOCOCCAL PNEUMONIA TREATED WITH AQUEOUS PENICILLIN AT TWELVE-HOUR INTERVALS*

PHILIP A. TUMULTY, M.D.,† AND GORDON ZUBROD, M.D.‡

BALTIMORE

THE efficacy of penicillin in the treatment of patients with pneumococcal lobar pneumonia is well established.[1, 2] However, the manner in which it may be employed to yield the best therapeutic results and with the least discomfort to the patient is still debated. It has been considered that to achieve maximum therapeutic response the blood concentration of penicillin must be maintained constantly at a level greater than the penicillin sensitivity of the particular organism.[3] Because of this assumption penicillin has generally been administered either in aqueous solution at frequent intervals or in some repository form. On the other hand, it has not been demonstrated either experimentally or clinically that this is necessary or desirable.[4] The relation of dosage frequency to therapeutic effectiveness has been examined in a streptococcal infection in mice treated with aqueous penicillin G.[5] The drug was just as effective when given once a day as when given more frequently. Similar results have been reported by others in the treatment of experimental infections in mice.[6–10] A few investigators have successfully employed aqueous penicillin given at infrequent intervals in pneumococcal lobar pneumonia,[1, 11] subacute bacterial endocarditis[12] and pharyngitis due to the beta-hemolytic streptococcus.[13] It seemed worth while, therefore, to extend these observations to the treatment of patients.

PLAN OF STUDY

Pneumococcal lobar pneumonia was chosen for this study because of the relatively sharp clinical end-point obtainable. A consecutive series of patients was treated with aqueous penicillin G given intramuscularly at twelve-hour intervals. The patients were admitted to the public wards of the Johns Hopkins Hospital between October, 1947, and May, 1948. Only cases of clear-cut pneumococcal lobar pneumonia were included, selection being based upon a characteristic history, physical and x-ray evidence of pulmonary consolidation, fever, leukocytosis and the presence of typable pneumococci in the sputum, nasopharynx or blood. There were 82 such cases. All were not seen by us, the care of the patients being primarily the responsibility of the resident staff. An effort was made to retain in the study all patients admitted with pneumococcal lobar pneumonia. However, because of misunderstandings, 3 patients were omitted from the series. They were only moderately ill and recovered uneventfully. Five patients were placed on intermittent intramuscular therapy after a short trial on the twelve-hour schedule. In 2 of these cases the regimen was altered because of the development of complications discussed below. In the remaining 3, discontinuance of the experimental dosage was considered in review to have been arbitrary, and the administration of 100,000 units of penicillin every two hours produced no dramatic alteration of the clinical course. All patients recovered. The total number receiving the trial dosage was therefore 79.

Cultures of the sputum, nasopharynx and blood were obtained before penicillin treatment was started. Most of the patients received a potassium salt of crystalline penicillin G of a single lot number, provided for these studies in 300,000-unit vials. The remainder were given the usual ward supply of penicillin, which varied somewhat as to degree of purity. The penicillin was given intramuscularly in distilled water. The initial dose was 300,000 units repeated at twelve-hour intervals until the temperature had remained normal for forty-eight hours, when 300,000 units was given at twenty-four-hour intervals for an additional forty-eight hours, unless there was some indication for more prolonged therapy. In 2 cases 600,000 units was given initially to severely ill patients.

No control series was established, the number of patients treated at this hospital each year making this impractical. However, there are available for comparison data on the patients with lobar pneumonia treated at this hospital with penicillin during the same period of 1945-1946 and 1946-1947. There were 69 patients in the 1945-1946 series. These were divided almost equally into three groups, receiving respectively 20,000, 40,000 and 80,000 units of aqueous penicillin intramuscularly at three-hour intervals. Fifty-eight patients were treated in 1946-1947 with penicillin in oil and beeswax. The majority of this group were given 300,000 units intramuscularly every twenty-four hours. A few initially received 300,000 units every twelve hours.

Comparative data for the three series regarding population sample, pneumococcal types and severity of disease are shown in Table 1. In general

*From the Department of Medicine and the Department of Pharmacology and Experimental Therapeutics, Johns Hopkins University School of Medicine and Johns Hopkins Hospital.

†Instructor in medicine, Johns Hopkins University School of Medicine; physician-in-charge, Medical-Surgical Group Clinic; assistant director of medical clinics and physician, Johns Hopkins Hospital.

‡Roche Fellow in Experimental Medicine and Therapeutics and instructor in medicine, Johns Hopkins University School of Medicine.

the pneumonia was considered to be of average and equal severity in the three groups studied. No deaths or serious complications occurred in the 1945-1946 or 1946-1947 series. However, neither of these groups comprised all the patients admitted because of pneumonia during the years concerned, since a few of the most severely ill patients were given massive amounts of penicillin or a sulfonamide in addition. Death and complications occurred in a few of these excluded patients. Therefore, the mortality and occurrence of complications in these two groups cannot be compared to those of the relatively consecutive 1947-1948 series. But it is valid to use these earlier groups as a basis of comparison of the rapidity of response to penicillin therapy.

TABLE 1. *Summary of Data.*

DATA	PATIENTS GIVEN AQUEOUS PENICILLIN (1945–1946)				PATIENTS GIVEN PENICILLIN IN OIL AND BEESWAX (1946–1947)	PATIENTS GIVEN AQUEOUS PENICILLIN (1947–1948)
	20,000 UNITS*	40,000 UNITS*	80,000 UNITS*	TOTAL*	300,000 UNITS†	300,000 UNITS‡
Total patients:	23	25	21	69	58	82
Male	14	16	14	44	45	53
Female	9	9	7	25	13	29
Negro	20	19	18	57	52	70
White	3	6	3	12	6	12
Age of patients:						
Under forty years	19	12	13	44	31	52
Forty to fifty-nine years	3	10	7	20	24	27
Sixty years and over	1	3	1	5	3	3
Severity of disease:						
Mild	4	0	1	5	14	14
Moderate	16	16	11	43	37	45
Severe	3	7	4	14	6	19
Critical	0	2	5	7	1	4
Duration of illness:						
Less than two days	7	3	4	14	8	11
Two to three days	11	13	9	33	26	36
Four to six days	5	5	6	16	18	29
Seven days or more	0	4	2	6	6	6
Indications of severity:						
Dehydration	3	4	3	10	18	28
Cyanosis	5	9	3	17	11	9
Jaundice	2	2	4	8	7	7
Disorientation	0	3	3	6	7	11
Shock	0	1	1	2	1	1
Leukopenia (white-cell count below 8000)	1	3	2	6	6	7
Bacteremia	1	5	5	11	8	10
Multilobar	3	8	8	19	12	17
Alcoholism	2	2	2	6	16	18
Cardiac failure	1	1	3	5	2	3
Cardiac disease	2	8	2	12	3	8
Diabetes	0	1	0	1	2	2
Hepatic insufficiency	1	1	0	2	1	3
Pregnancy	1	0	0	1	2	1
Pneumococcal types:						
1–8	7	13	9	29	31	45
Higher types	5	9	6	20	19	27
Untyped	4	6	4	14	8	7
None found	2	2	2	6	0	3
Patients receiving sulfonamides prior to admission	1	1	2	4	3	1

*Every three hours.
†Every twenty-four hours.
‡Every twelve hours.

RESULTS

The response of the patients to the several regimens of penicillin is shown in Table 2 and expressed in terms of total febrile days, total days in bed and period of hospitalization. Within the limitations of this type of clinical study there was no superiority in the response of patients receiving frequent dosages of aqueous penicillin or repository penicillin as contrasted with the response of those receiving aqueous penicillin G at twelve-hour intervals. What minor differences there were favored the latter schedule.

Two deaths occurred in the 82 patients treated during 1947-1948. One happened three hours after admission in a patient with severe hyperthyroidism, auricular fibrillation and cardiac failure after a single injection of 900,000 units of aqueous penicillin. The other occurred seven hours after admission in a patient with a severe head injury who was given 100,000 units of aqueous penicillin intramuscularly at three-hour intervals. Two patients in this group developed complications of their infection. Pneumococcal meningitis appeared in one patient sixteen hours after admission. He had a pneumonia due to a pneumococcus Type 2 with bacteremia. The other complication appeared in a fifty-nine-year-old Negro known to have had chronic pulmonary disease for twelve years. He was admitted with pneumonia of the right upper and

middle lobes due to a Type 7 pneumococcus with bacteremia. Thirteen days after admission cavitation was noted in the right middle lobe. There is a reasonable possibility that both these complications had their inception before the institution of therapy. With the appearance of these complications, the patients were given massive doses of penicillin and sulfonamides. Recovery occurred in both cases.

Only a single patient in the 1947-1948 series developed a penicillin reaction. This followed the use of the highly purified penicillin G and consisted of fever and exfoliative dermatitis on the twelfth day of therapy. No severe local reactions occurred. With aqueous "ward-stock" penicillin at three-hour intervals, the systemic reaction rate was 10 per cent, and with penicillin in oil and beeswax it was 19 per cent. An additional 25 per cent of patients had a local reaction to penicillin in oil and beeswax, characterized by pain, redness and edema at the site of injection.

TABLE 2. *Duration of Fever, Bed Care and Hospitalization after Start of Penicillin in Recovered Patients.*

DATA	PATIENTS GIVEN AQUEOUS PENICILLIN (1945–1946)				PATIENTS GIVEN PENICILLIN IN OIL AND BEESWAX (1946–1947)	PATIENTS GIVEN AQUEOUS PENICILLIN (1947-1948)
	20,000 UNITS*	40,000 UNITS*	80,000 UNITS*	TOTAL*	300,000 UNITS†	300,000 UNITS‡
Total cases	—	—	—	69	58	75§
Duration of fever:						
One day or less	8	1	6	15	10	29
Two days	8	5	6	19	6	18
Three days	2	6	3	11	5	8
More than three days	5	13	6	24	37	20
Days in bed:						
Six or less	10	4	7	21	14	27
Seven to twelve	13	13	5	31	33	41
Thirteen or more	0	5	9	17	11	7
Days in hospital:						
Eight or less	6	1	1	8	6	15
Nine to sixteen	16	14	12	42	33	40
Seventeen or more	1	10	8	19	19	20

*Every three hours.
†Every twenty-four hours.
‡Every twelve hours.
§Excludes 2 deaths, 2 complications and 3 patients who did not start on experimental regimen.

DISCUSSION

Penicillin G in aqueous solution given at twelve-hour intervals was found to be a highly effective means of treating pneumococcal lobar pneumonia. Death and complications each occurred in but 2.4 per cent of the 82 cases. In terms of the number of febrile days, the number of days in bed and the period of hospitalization, the administration of penicillin at twelve-hour intervals was at least as effective as the schedules designed to maintain a constant penicillin blood concentration.

A single dose of 300,000 units of aqueous penicillin G given intramuscularly maintains the concentration in the blood above 0.1 unit per cubic centimeter for only five or six hours,[14] so that for about half the time these patients had little if any circulating penicillin. Since therapeutic response was so satisfactory it appears questionable whether a constant blood level of penicillin is necessary in the treatment of pneumococcal pneumonia. The employment of repository forms such as penicillin in oil and beeswax or procaine penicillin, or the administration of aqueous penicillin at short intervals, is unnecessary in the therapy of lobar pneumonia. Whether infrequent dosage of penicillin in aqueous solution will be effective in the treatment of other infections has not been determined. The experimental work suggests that it would be effective. However, only careful clinical observation will demonstrate how universally this method of therapy may be safely applied.

It is quite likely that the amounts of penicillin G employed in this study were in excess of what is needed for adequate therapy of pneumococcal lobar pneumonia. A total dose of 90,000 to 300,000 units of aqueous penicillin will cure some patients with lobar pneumonia.[1] However, there seems to be little justification for determining the minimal effective dosage of penicillin in a disease with a potential mortality of 30 per cent. This position is supported by the infrequency of complications accompanying the use of fairly brisk dosage and by the lack of toxicity of pure penicillin G. It has been shown in streptococcal infections in mice that a large initial dose of penicillin G keeps the mice alive much longer than the same dose split into smaller fractions, even though the dose is too small to save any of the mice ultimately.[5] It seems wise to use similar large initial priming doses of penicillin G in the treatment of pneumococcal pneumonia and other infections. Such priming doses are an essential part of the successful use of the sulfonamides, and it is a curious circumstance that a similar loading device has not been carried over to the penicil-

lin treatment of infections. In the use of slowly absorbed penicillin preparations such as penicillin in oil and beeswax and procaine penicillin or indeed when penicillin in aqueous solution is given in equal fractions at three-hour intervals, the advantage of a priming dose is lost.

Summary and Conclusion

Two hundred and six cases of pneumococcal lobar pneumonia treated with penicillin are reported. In these cases 79 patients were treated with aqueous penicillin G given intramuscularly every twelve hours, 69 received aqueous penicillin intramuscularly every three hours, and 58 were given penicillin in oil and beeswax.

The patients who were treated with 300,000 units of aqueous penicillin G intramuscularly every twelve hours fared as well as those on the usual schedules of administration.

The intramuscular administration of 300,000 units of aqueous penicillin G every twelve hours is the treatment of choice for pneumococcal lobar pneumonia.

We are indebted to Dr. K. K. Chen, of Eli Lilly and Company, Indianapolis, Indiana, for a generous supply of the potassium salt of pure penicillin G.

References

1. Tillett, W. S., Cambier, M.J., and McCormack, J. E. Treatment of lobar pneumonia and pneumococcal empyema with penicillin. *Bull. New York Acad. Med.* **20**:142-178, 1944.
2. Meads, M., Harris, H. W., and Finland, M. Treatment of pneumococcal pneumonia with penicillin. *New Eng. J. Med.* **232**:747-755, 1945.
3. Eagle, H. Speculations as to therapeutic significance of penicillin blood level. *Ann. Int. Med.* **28**:260-278, 1948.
4. Marshall, E. K., Jr. Dosage schedule of penicillin in bacterial infections. *Bull. Johns Hopkins Hosp.* **82**:403-407, 1948.
5. Zubrod, C. G. Comparative efficiency of single and multiple dosage regimens of penicillins. *Bull. Johns Hopkins Hosp.* **81**:400-410, 1947.
6. Jawetz, E. Dynamics of action of penicillin in experimental animals: observations on mice. *Arch. Int. Med.* **77**:1-15, 1946.
7. White, H. J., Lee, M. E., and Alverson, C. Therapeutic effectiveness of single oral doses of penicillin. *Proc. Soc. Exper. Biol. & Med.* **62**:35, 1946.
8. White, H. J., Baker, M. J., and Jackson, E. R. Therapeutic effectiveness of single and divided doses of penicillin in streptococcal infection in mice. *Proc. Soc. Exper. Biol. & Med.* **67**:199-203, 1948.
9. McLeod, C. M., and Stone, E. R. Differences in nature of antibacterial action of sulfonamides and penicillin and their relation to therapy. *Bull. New York Acad. Med.* **21**:375-388, 1945.
10. Gibson, C. D., Jr. Comparative effectiveness of two penicillin treatment schedules in pneumococcal infections in mice. *Proc. Soc. Exper. Biol. & Med.* **67**:278-280, 1948.
11. Conference on therapy: treatment of pneumonia. *Am. J. Med.* **4**: 423-435, 1948.
12. Bloomfield, A. L., and Halpern, R. M. Penicillin treatment of subacute bacterial endocarditis: some problems. *J. A. M. A.* **129**:1135-1141, 1945.
13. Jawetz, E. Dynamics of action of penicillin: time-dose relationship in human streptococcic disease. *Arch. Int. Med.* **81**:203-208, 1948.
14. McDermott, W., Bunn, P. A., Benoit, M., DuBois, R., and Reynolds, M. E. Absorption, excretion and destruction of orally administered penicillin. *J. Clin. Investigation* **25**:190-210, 1946.

THE USE OF TESTOSTERONE IN THE TREATMENT OF DEPRESSIONS*

Mark D. Altschule, M.D.,† and Kenneth J. Tillotson, M.D.‡

BOSTON AND WAVERLEY, MASSACHUSETTS

SEX hormones and related substances have been used in the treatment of depressions for a number of years. Although the use of estrogenic substances of various types has yielded disappointing results in deeply depressed women, the injection of testosterone has been known for a decade or more to cause remission in male patients with depressions, provided large doses are used. Danziger and Blank[1] reviewed the earlier clinical literature bearing on this point; a more recent review by Danziger et al.[2] is also available. The rationale for the use of testosterone in the past has been that of replacement therapy in men past middle life. However, the fact that small doses are ineffective should have suggested the inadequacy of this concept.

Recent studies have shown that electroconvulsive therapy gives rise to effects resembling those caused by the action of some steroid hormones.[3–8] The effects of electroshock therapy that resemble those occurring after the injection of steroid hormones consist, briefly, in fall in plasma protein level, decrease in lymphocytes in the peripheral blood and reduction in eosinophil count, increased diuretic response to water and evidence of extracellular retention of water and sodium. The administration of desoxycorticosterone and of progesterone in large doses having failed here to cause remission of mental symptoms, it was decided to use testosterone; all three of the hormones mentioned have the effect of causing salt and water retention, but only the last has an additional marked anabolic action. The present report summarizes experience here to date.

Material and Methods

Thirty-one patients, ranging in age from thirty-one to seventy-four years, were given testosterone by injection. They included patients with depressed phase of the manic-depressive psychosis, with involutional psychoses with depression, with reactive depressions and, in 1 case, schizophrenia with a strong depressive component. Only 3 were women, 2 of them having involutional psychoses and the third a manic-depressive psychosis in the depressed phase.

*From the Clinical Services and the Laboratories of Clinical Physiology, McLean Hospital, Waverley, Massachusetts, and the Departments of Medicine and Psychiatry, Harvard Medical School.

†Assistant professor of medicine, Harvard Medical School; director of research in clinical physiology, McLean Hospital.

‡Formerly, associate in psychiatry, Harvard Medical School; formerly, psychiatrist-in-chief, McLean Hospital.

Testosterone was given intramuscularly in doses of 50 mg. daily for two or three weeks; in most cases it was given in two doses of 25 mg. each day. In 1 case the material was given for six weeks, discontinued for a month and given again for a month. After discharge some of the patients were given methyl-testosterone orally, 30 mg. per day. Seven of the patients received electroshock therapy at approximately the same time as the injection of the hormone; 7 had had shock therapy previously, and 6 were given it subsequently.

Observations

Clinical Results

Of the 7 patients, all men, given testosterone at approximately the same time as shock therapy, all improved and were discharged.

In the 17 patients who had not had shock therapy before receiving testosterone, the following effects were noted: improved (discharged), 11 (10 men, 1 woman); discontinued, 2 men; and not improved, 4 men.

Of the 4 men not improved by injection of testosterone, 3 subsequently were given electroshock therapy. All 3 improved, 1 after six treatments in the course of a month, 1 after four treatments a week apart, and 1 after thirty-two shocks given over a period of several months.

Seven patients were given testosterone during relapse after improvement with electroconvulsive therapy, with the following results: 3 men given testosterone one month after relapse were improved (discharged); neither of 2 women given testosterone one month after relapse improved; 1 man given testosterone five months after relapse improved (discharged); and 1 man given testosterone twelve months after relapse showed no improvement.

In 2 patients in this group who recovered after getting testosterone, relapse occurred after the hormone had been discontinued. Brief abstracts of these cases are as follows:

Case 1. A 39-year-old man with a reactive depression was first seen in August, 1946. After five treatments of electroshock, given between December 10 and 20, he improved and gained 8 pounds. Later in that month he suffered a relapse. Eight additional electroshock treatments were given from January 1 to 17, 1947, with improvement and another gain of 8 pounds in weight. Another relapse occurred, and the patient was therefore given 25 mg. of testosterone twice a day from February 8 to 21. He improved, gained 6 pounds and was discharged. A third relapse occurred in May.

Case 2. A 54-year-old man with a manic-depressive (depressed) psychosis was seen in May, 1946. After six electroshock treatments in July he was improved, but during that month he relapsed. From January 17 to 31, 1947, seven electroshock treatments were given, with improvement and a gain of 14 pounds in weight. Another relapse occurred in February, and 25 mg. of testosterone was given twice a day from March 4 to 26. The patient improved and gained 15 pounds, but suffered a further relapse during the following month. In May, improvement and a gain of 9 pounds in weight followed fourteen electroshock treatments.

All 3 patients in this group who did not respond to testosterone were subsequently given shock therapy. The 2 women improved after twelve shocks given over a period of five weeks; they soon relapsed, however. Still another course of shock therapy was then given to 1 of these patients, who died during the treatment, with massive hemorrhage of an adrenal gland. The man in this group improved after six shocks and maintained his improvement for two months before relapsing.

Side Reactions

Two patients could not receive the full course of treatment with testosterone because of the development of edema, tachycardia and severe dyspnea; both were known to have had mild congestive failure previously. Digitalis and ammonium chloride did not influence these symptoms, which remained markedly discomforting for approximately a week. Two other patients exhibited mild edema and shortness of breath; they had no evidence of heart disease.

Two patients exhibited gynecomastia during the course of treatment; one was a man of forty-four who many years previously had had a testicle removed for tumor, and the other was a man of sixty-three with no unusual previous findings in history or physical examination.

The women showed heavy overgrowth of facial hair.

Discussion

The earlier work with testosterone[1, 2] involved the use of the hormone as a form of replacement therapy in men with involutional melancholia. Some authors[1, 2] gave as many as six injections, each of 25 mg. of the hormone, each week for more than twelve weeks. In the present study the rationale of treatment was different in that the hormone was used as a substance with marked anabolic effects and not as a specific sex hormone.

The effect of testosterone is largely or entirely on the affective disorder; paranoid or other serious disturbances in thinking were not changed, and neurotic manifestations were influenced but little. The disappearance of depression, confusion and retardation, however, was definite.

Analysis of the clinical results is difficult. The 7 patients who received electroconvulsive therapy at approximately the same time as the injections of testosterone afford no data for judging the value of the latter. These patients were given testosterone when the course of shock therapy was interrupted by fractures or because the clinical staff believed that the patients' histories raised the possibility of early relapse after shock. In the 11 patients in whom improvement occurred when they were given testosterone not in relation to shock therapy, it is likewise difficult to evaluate the role of the hormone.

The natural history of depressions includes high rates of remission irrespective of therapy; the patients treated here were all receiving psychotherapy during the period of administration of testosterone, and all but 1 were hospitalized. Accordingly, the role of testosterone in relation to clinical improvement cannot be stated with certainty in spite of the fact that individual patients appeared to show no evidence of improvement until after the drug was started. The failures in this group are, however, of interest. They include 2 patients who could not receive the full course of therapy because of aggravation of the manifestations of congestive failure; 4 others who received the full course of injections did not respond, and 3 were then given shock therapy. One improved after thirty-two shocks given over a period of several months, and the other 2 improved after short courses of shock therapy. The last 2 of these patients must be regarded as definite cases of failure of testosterone therapy, but the first patient who received testosterone for only two weeks and then shock therapy for several months need not be.

The results in the patients who received testosterone after relapse following improvement due to electroshock therapy show that the effects of testosterone and of electroshock are interchangeable, at least in some cases. The only failure in the men was a patient who received testosterone a year after receiving shock therapy; he subsequently improved again with shock therapy. Possibly a longer course of testosterone should have been given in his case if one can judge by the results in the man who was given testosterone five months after shock; this patient required six weeks of testosterone for striking benefit to be obtained, although he showed some improvement after two weeks. The 2 women who failed to respond to testosterone given a month after relapse following improvement with shock therapy received the drug for three weeks; both required five weeks of shock therapy for temporary remission of their depressions.

It is possible, judging from the earlier work cited above,[1, 2] that longer courses of treatment with testosterone would have helped some of the patients who showed no improvement in the present study. Long courses have not been employed here as a rule because of the untoward cosmetic effects in women, and because of the more rapid improvement caused by electroshock therapy in patients who might be suicidal; the expense of unnecessary prolongation of hospitalization was also taken into account.

The untoward effects of testosterone therapy — that is, hirsutism in women and excessive salt retention in patients with myocardial insufficiency — were expected. The occasional occurrence of gynecomastia resembles that reported by McCullagh and Rossmiller[9] in patients receiving androgen therapy.

The fact that the effects of testosterone and of electroshock therapy are interchangeable supports the concept that the physiologic changes indicative of increased production of some steroid hormones seen during shock therapy are causally related to remission of mental disease caused by the latter. Since the steroid hormone effects involved are not those of salt and water retention but seem to be an anabolic reaction, it is possible that the effects of electroshock therapy are primarily reparative and, if at all destructive, ony incidentally so. This concept may explain the fact that affective disorders occurring during the course of such destructive processes as general paresis and multiple sclerosis are benefited by shock therapy.

Summary and Conclusions

The administration of testosterone in large doses is followed by remission of mental symptoms in some patients with all types of depression. The hormone acts apparently not as a specific sex hormone but as a substance with strong anabolic effects. In some patients it can be shown that the effects of electroshock and of testosterone are interchangeable, a phenomenon that suggests that the beneficial effects of convulsant therapy are the results of increased production of some steroid hormones. It is not unlikely that the favorable effects of electroshock therapy are reparative and not destructive.

References

1. Danziger, L., and Blank, H. R. Androgen therapy of agitated depressions in the male. *M. Ann. District of Columbia* **11**:181-183, 1942.
2. Danziger, L., Schroeder, H. T., and Unger, A. A. Androgen therapy for involutional melancholia. *Arch. Neurol. & Psychiat.* **51**:457-461, 1944.
3. Altschule, M. D., Cram, J. E., and Tillotson, K. J. Fall in plasma protein level associated with rapid gain in weight during course of electroshock therapy. *Arch. Neurol. & Psychiat.* (in press).
4. Altschule, M. D., and Tillotson, K. J. Effects of electroconvulsive therapy on diuretic response to water in psychotic patients. *Arch. Neurol. & Psychiat.* (in press).
5. Altschule, M. D., Ascoli, I., and Tillotson, K. J. Changes in extracellular fluid and plasma volumes during course of electroshock therapy. *Arch. Neurol. & Psychiat.* (in press).
6. Altschule, M. D., and Tillotson, K. J. Effect of electroconvulsive therapy on water metabolism in psychotic patients. *Am. J. Psychiat.* (in press).
7. Altschule, M. D., Altschule, L. H., and Tillotson, K. J. Unpublished data.
8. Altschule, M. D., Parkhurst, B. H., and Tillotson, K. J. Decrease in blood eosinophilic leukocytes after electrically induced convulsions. *J. Clin. Endocrinol.* (in press).
9. McCullagh, E. P., and Rossmiller, H. R. Methyl testosterone. I. Androgenic effects and production of gynecomastia and oligospermia. *J. Clin. Endocrinol.* **1**:496-502, 1941.

POLLEN SENSITIVITY IN 100 ASTHMATIC CHILDREN

LEWIS WEBB HILL, M.D.*

BOSTON

IT IS well known that pollen sensitivity is common in asthmatic children. The full importance of this, however, is not generally appreciated, and in most textbooks and other discussions of asthma in childhood more emphasis is given to such allergens as house dust, animal danders and foods than to pollens. In my experience pollen sensitization and the common infectious cold are the two most frequent causes of asthmatic attacks in children, and the number of cases that are helped by removal of a cat, a mattress or some food is small indeed when compared with those in which the attacks are precipitated by pollen or infectious colds.

In an allergy practice or clinic devoted to adults, patients with uncomplicated hay fever predominate. With children this is not so, and of 100 consecutive cases of respiratory allergy from my office files there were 80 cases of asthma and only 20 of hay fever. A high proportion of children who begin with hay fever have pollen asthma after a few seasons.

The pollen season in New England lasts about six months (from April 15 to October 10), and in children the majority of attacks of asthma occurring during this period are due to pollen.

Of 100 asthmatic patients between the ages of three and twelve years tabulated in alphabetic order from my office records, 70 gave positive scratch tests to one or more pollens. In contrast to positive tests with foods (about 20 per cent etiologic), a positive test with pollen as a rule indicates clinical sensitivity. Among the 70 children who gave positive reactions to pollen there were 225† positive tests. Of these, approximately 90 per cent were thought to be of clinical significance (Table 1).

INTRACUTANEOUS TESTS

As a rule, skin sensitivity to pollen in children is not of such high degree as that in adults. The younger the child and the shorter time he has had symptoms the more likely is this to be so. The more delicate intracutaneous test often reveals sensitization when the scratch test will not. It is my practice first to do scratch tests with pollens as a routine on all asthmatic patients, which are followed by intracutaneous tests if the child has symptoms during the season of any pollen and fails to react to it by scratch test. In children the scratch test can by no means be relied upon to demonstrate pollen sensitization.

Intracutaneous tests were done on 20 of the 30 children who failed to give a positive scratch test to any pollen. There were positive reactions to one or more pollens in 14. Of the 100 children under discussion, therefore, 84 gave positive tests, either scratch or intracutaneous, to pollen. All the positive intracutaneous tests were presumably of clinical significance, since they were done only on a selected group, whose histories suggested clinical sensitivity.

TABLE 1. *Positive Scratch Tests to Pollens in 100 Asthmatic Children.*

POLLEN	No. OF POSITIVE TESTS
Birch	26
Maple	18
Ash	3
Elm	5
Oak	10
English plantain	4
Grass pollen	40
Ragweed	45

TREE POLLEN

In New England birch and oak are the most important trees as far as asthma is concerned. Maple pollen gives a good many positive reactions, but is relatively unimportant as a cause of asthma, for it is heavy and sticky and is therefore not disseminated as readily as birch and oak pollen.

GRASS POLLEN

Twenty-two patients reacted to all the four grass pollens employed in scratch tests; 18 reacted to one or more, but not to all. There were 28 patients who gave positive intracutaneous but negative scratch tests to grass pollen. There were therefore 68 out of 100 who reacted to grass pollen. Positive scratch tests were about equally divided between the four grasses, as follows: timothy, 30; red top, 27; June grass, 28; and orchard grass 29.

RAGWEED

In 28 patients there was a positive intracutaneous test to ragweed with a negative scratch test. There were therefore 73 out of the 100 children who reacted to this pollen.

ASSOCIATED SENSITIZATIONS

There was no child who reacted to pollen who did not also react to other environmental allergens. House dust, cat hair and mold (alternaria or hormodendrum) were the most common, with 65 positive reactions to dust, 39 to cat hair, and 38 to

*Associate in pediatrics, Harvard Medical School; visiting physician, Children's Hospital.

†The discrepancy between this figure and the sum total of the figures given in the table is because tests were done with four different grass pollens, and usually more than one gave positive tests.

mold. I doubt whether uncomplicated pollen allergy exists in asthmatic children, and it is uncommon in children with hay fever. This is a very different situation from that in adults, among whom uncomplicated pollen allergy in hay fever is common.

Summary and Conclusions

In a series of 100 asthmatic children between the ages of three and twelve years, there were positive skin reactions to one or more pollens in 84.

Approximately 90 per cent of these reactions were of clinical significance.

The scratch test, particularly in children, is frequently not delicate enough to demonstrate pollen sensitization.

Asthmatic children who are sensitized to pollen are always sensitized to other environmental allergens as well.

The importance of pollen sensitization in the asthma of children is not sufficiently appreciated. In New England, pollen is the most important factor contributing to asthma in children during the spring, summer and early fall — approximately six months of the year.

319 Longwood Avenue

MEDICAL PROGRESS

BAL (Concluded)*

Raymond V. Randall, M.D., and Albert O. Seeler, M.D.†

BOSTON

Arsenic

Stocken and Thompson[39] found that the topical application of BAL to lewisite burns was followed by an increase in the urinary excretion of arsenic. These authors then demonstrated that parenteral administration of BAL saved rats poisoned by the application of lethal amounts of lewisite to the body surface. Harrison and his co-workers[40] concluded from their experiments on dogs that the most effective way to treat extensive lewisite burns was to use BAL ointment to combat the local skin effects of lewisite, and, at the same time, to use the compound parenterally to combat the effects of the absorbed arsenic.

Eagle et al.[4] have shown that BAL applied to the skin or given parenterally was effective in the treatment of acute and subacute arsenic poisoning in various animals. In animals so treated, there was a striking increase in the rate of urinary arsenic excretion with the peak of excretion coming two to four hours after the administration of BAL. In conjunction with these findings, Riker and Rosenfield,[41] in studies on the effect of BAL on mapharsen-poisoned cats, found that it increased the concentration of arsenic in the plasma. After the injection of BAL, a high level of plasma arsenic was reached within one hour and a peak at two hours. These results were considered to be in accord with the concept that BAL effects a withdrawal of arsenic from the tissues.

Peters and Stocken[42] prepared a complex from mapharsen and BAL and found it to be more toxic than either BAL or arsenic alone. However, when this complex was injected together with one mole excess of BAL, it was only one fifth as toxic as arsenic alone. The authors suggested that this phenomenon could be explained by the dissociation of the mapharsen-BAL complex to release arsenic in areas where it could cause the maximum toxic effects. However, when excess BAL was present, the extent of dissociation and, consequently, the toxicity of the complex were decreased. Another explanation may be that one mole of arsenic can unite with one or two moles of BAL to form complexes of greatly different properties, as cadmium and mercury do.[43, 44] Even more paradoxical are the findings of Koppanyi and Sperling,[45] who gave BAL to rabbits that had received nonlethal doses of sodium *arsenite*, and found that the animals developed intense central-nervous-system stimulation. The same amounts of arsenite or BAL alone did not produce symptoms, and massive doses of a preformed arsenite-BAL complex were likewise nontoxic. Similar effects were not noted with arsenates or organic arsenicals. On the basis of these experiments, the authors warned that persons poisoned by arsenites (such as Fowler's solution) might conceivably develop undesirable side effects if treated with BAL.

Several investigators have studied the effect of BAL and related compounds on arsine poisoning. Inhalation of this extremely toxic gas may cause intense hemolysis of the red blood cells, with subsequent hemoglobin nephrosis. It is also an inhibitor of tissue respiration. Kensler et al.[46] found that

*From the Department of Industrial Hygiene, Harvard School of Public Health.

This study was aided by a grant from the Medical Advisory Committee of the American Petroleum Institute.

†Assistant professor of industrial medicine, Harvard School of Public Health.

BAL was ineffective in preventing in vitro hemolysis of red blood cells by arsine, whereas a related compound, BAL ethyl ether (2, 3-dimercaptopropylether), worked very well. These findings were borne out in arsine inhalation poisoning in rabbits and cats, in which BAL ethyl ether given immediately after exposure was found to be an effective agent, whereas BAL was useless.[46, 47] Because of its great toxicity, it seems unlikely that BAL ethyl ether will be of value in the treatment of arsine poisoning among human beings. Levvy[48] found that another compound, ethane-1:2-dithiol, given intraperitoneally decreased the toxicity of arsine for mice. This compound was effective when given as long as three to four hours after exposure to arsine.

Hughes,[49] studying the effects of lewisite on the rabbit eye, found that it produced rapid necrosis of the cornea and conjunctiva, and that arsenic liberated from the lewisite rapidly penetrated into the chambers of the eye. BAL, in a 5 per cent ointment, proved to be a satisfactory antidote because it not only detoxified the lewisite at the surface of the eye but also rapidly penetrated the tissues of the eye to unite with the arsenic there. Because of the rapid action of lewisite, the ointment had to be applied within two minutes of the lewisite to protect the eye completely; if applied after thirty minutes, permanent damage from the lewisite always occurred. BAL itself in ointment concentrations greater than 5 per cent was found to produce a transient opacification of the superficial layers of the cornea.

Clinical Uses

After it became apparent that BAL was effective against arsenic poisoning in animals, it was tried in various clinics in the treatment of accidental arsenic poisoning and the undesirable side effects occurring in arsenotherapy.

BAL has been used extensively in the treatment of arsenical dermatitis with good results.[30, 50, 51] In severe cases, edema, fever and pruritus disappear or greatly decrease in twenty-four hours, and complete recovery may occur within two weeks. However, some patients respond only partially, or may relapse and require another course of BAL, whereas others may show no improvement at all. Occasionally, as has been noted, abscesses, which are probably due to secondary infection, occur at the sites of intramuscular injection. Although inunctions of BAL are beneficial in dermatitis, they are not so effective as intramuscular injections and may cause skin sensitization to BAL.

Eagle and Magnuson[30] have reported the results of BAL therapy in 55 cases of arsenical encephalitis, usually a lethal complication of arsenotherapy. Only 11 patients died, and in 5 of these BAL therapy was not started until nine to seventy-two hours after the onset of encephalitis. These workers likewise studied the value of BAL in the treatment of 16 patients with so-called post-arsenical jaundice. Only 5 of the 16 patients recovered within ten days of initiation of therapy. The results in this small series of cases suggest that BAL is not very effective in postarsenical hepatitis, but it must be remembered that some authorities consider this condition to be an infection rather than a toxic manifestation of arsenic.

BAL has been of value in some blood dyscrasias associated with arsenotherapy. Eagle and Magnuson[30] reported the failure of BAL to affect the course of 3 cases of aplastic anemia and 1 case of agranulocytosis with thrombocytopenia occurring in persons undergoing arsenotherapy. On the other hand, 10 cases of agranulocytosis responded promptly to BAL — all showing an increase in granulocytes by the second day and a normal count by the seventh day. Holley[52] reported equally good results in 12 cases of arsenical agranulocytosis treated with BAL. Schrumpf[53] reported a favorable result following BAL in a patient with thrombocytopenic hemorrhages associated with neoarsphenamine therapy. In 11 days there was an increase in the platelet count from 2500 to 280,000.

BAL has been used in 4 patients who had received massive doses of mapharsen by error.[30] Three patients had received doses of between 400 and 600 mg. of mapharsen each and made uneventful recoveries after the administration of BAL. The fourth patient was given 1200 mg. of mapharsen and died after inadequate BAL treatment in spite of an initially favorable response.

Several cases of optic complications following arsenotherapy have been treated by BAL. Eagle and Magnuson[30] reported a good response in 3 of 6 patients with visual impairment associated with tryparsamide therapy. Friedenberg[54] observed that a tabetic patient in whom a decrease in visual fields followed tryparsamide therapy had a return of vision after the administration of BAL.

Woody and Kometani[32] have reported on the use of BAL in a large group of infants and children. They treated 42 infants and children who had ingested arsenic-containing substances. Of these, 22 had taken potentially lethal amounts of arsenic. There were no deaths in this series, and in all cases signs and symptoms of arsenic poisoning disappeared within twelve hours of the initiation of BAL therapy.

Mercury

It has been shown that BAL can both prevent the inhibitory effect of mercuric chloride on a brain brei preparation, and reactivate the enzyme succinoxidase after mercury inactivation.[55, 56]

Studies with BAL, BAL glucoside and the monothiol thiosorbitol[44] demonstrated that all three could protect rabbits against acute mercury poisoning if therapy was begun properly. Quantitative evalu-

ation of the protective activity of these compounds showed that the dithiols were far superior to thiosorbitol. BAL glucoside proved to be more active than BAL itself. Rabbits receiving inadequate doses of the thiol compounds died of renal failure. It is interesting to note that although BAL and BAL glucoside can also prevent the development of fatal renal damage in dogs after large intravenous doses of mercuric chloride, some of the animals succumbed to acute pulmonary edema. When mercuric chloride was given orally, BAL and BAL glucoside were also effective in preventing renal deaths, but some of the animals died of a hemorrhagic gastroenteritis.

Because of the extensive use of sodium formaldehyde sulfoxylate as an antidote for mercury poisoning, Stocken[57] compared the effectiveness of this compound with that of BAL. He found that BAL fully protected rats from lethal doses of mercuric chloride, whereas sodium formaldehyde sulfoxylate proved ineffective under similar conditions.

Human Poisoning

Longcope and Luetscher[58] have used BAL extensively in the treatment of acute poisoning in man after the ingestion of mercury bichloride. They reported that of 42 patients suffering from acute mercury poisoning in whom BAL was used, only 2 died. These 2 patients were in a group of 5 cases in which BAL was not started until six to forty-two hours after the ingestion of mercury. Not one of 37 patients receiving BAL within four hours died, regardless of the severity of symptoms or the amount of mercury taken. This stresses the importance of instituting BAL therapy at the earliest possible moment. However, one should not overlook the value of general supportive measures such as intravenous fluids and transfusions. The schedule of BAL treatment for mercury poisoning recommended by the Council on Pharmacy and Chemistry of the American Medical Association (as listed below under dosage schedules) is based on the experience of these authors.

Effects on Mercurial Diuretics

BAL can prevent the occurrence of convulsions and cardiac arrhythmias produced in experimental animals by the administration of mercurial diuretics. It can also prevent the characteristic diuresis produced by these drugs.[59–64] In contrast to BAL, which inhibits both the toxic and the diuretic effects, the monothiols cysteine and glutathione can protect the hearts of animals against toxic effects of the mercurial diuretic mersalyl without abolishing its diuretic effect.[65] Further evidence that monothiols reduce the toxicity of mercurials is supplied by the work of Lehman,[66] who synthesized a diuretic containing thioglycollic acid that proved to be only one-four-hundredth to one-six-hundredth as toxic as comparably effective mercurial diuretics. These findings suggest the possibility of using certain monothiols either in chemical combination or by simultaneous administration to abolish the undesirable effects of mercurials without impairing their diuretic action. However, each mercurial compound must be thoroughly investigated before clinical use in such a manner, because Cohen[67] has reported that a number of alkyl mercuric thioglycollates can produce severe central-nervous-system effects.

Acrodynia

Because mercury has recently been suspected of having a causal relation to acrodynia, Bivings and Lewis[68] gave a twelve-day course of BAL to an infant in whom the diagnosis of acrodynia had been made. It is of interest that this infant had been given twelve doses of calomel and rhubarb a number of weeks before the onset of the signs and symptoms that led to the diagnosis of acrodynia. The urine showed a mercury concentration of 100 microgm. per 100 cc. before the initiation of BAL therapy. Eight days after the last dose of BAL, the urine was found to be free of mercury, and a week or two later all signs and symptoms of acrodynia had disappeared.

GOLD

Thompson and Whittaker[55] found that BAL can protect the brain pyruvate oxidase system from the toxic effects of gold. However, the striking difference in effectiveness between dithiols and monothiols noted in arsenic poisoning was not found: glutathione gave the same degree of protection against gold inhibition as BAL did.

Gold therapy is used extensively in rheumatoid arthritis although it is a potentially toxic agent capable of causing pruritus, dermatitis, stomatitis, agranulocytosis, thrombocytopenia and other disorders. BAL has been used in several clinics to treat these complications of gold therapy. Ragan and Boots[69] reported a series of 5 patients with gold dermatitis who were treated with BAL. In 4 patients there was prompt subsidence of pruritus, and the rash disappeared within one month of BAL treatment. No change took place in the fifth patient's condition. All patients showed an increase in excretion of urinary gold, concurrent with the administration of BAL. Four of the patients had a recurrence of arthritic symptoms shortly after the BAL treatment, offering some support to the contention that chrysotherapy has only a temporary effect on rheumatoid arthritis. Cohen et al.[70] found that BAL caused prompt recovery in 5 cases of gold dermatitis of short duration. The authors attribute these excellent results, in part, to the fact that BAL therapy was instituted early in each case. Margolis and Caplan[71] state that in their experience BAL was of marked benefit in a case of severe stomatitis and a case of dermatitis and sto-

matitis, of possible benefit in 2 cases of dermatitis and of no value in a case of dermatitis of moderately short duration.

Lockie and his co-workers[72] found BAL to be strikingly effective in the treatment of 2 patients with blood dyscrasias following chrysotherapy. A patient with thrombocytopenia, bleeding gums and coma from a possible subarachnoid hemorrhage responded to BAL within several days and had a concurrent increase in platelets from 15,000 to 120,000. The other patient had agranulocytosis, and within seventy-two hours after initiation of BAL therapy the granulocytes increased from zero to 17 per cent, and by the seventh day they had increased to 45 per cent.

Lead

Although BAL can reverse the lead inhibition of the sulfhydryl-containing enzyme, succinoxidase,[56] and can increase the urinary output of lead, there is no satisfactory evidence that it is of value in the treatment of lead poisoning.

Animal Studies

Braun et al.[73] concluded that BAL was ineffective in both acute and chronic experimental lead poisoning. They gave BAL to rabbits poisoned by a single large dose of lead nitrate and to others poisoned by multiple small doses of lead nitrate, and in each case the mortality in animals treated with BAL was greater than that in animals receiving lead nitrate alone. This suggested that BAL had an additive effect. Germuth and Eagle[74] likewise found that BAL failed to protect rabbits against acute or chronic lead poisoning, and in one group of animals found that BAL hastened the onset of death. BAL did cause a marked increase in the urinary excretion of lead, but this response decreased with each subsequent injection. The period of increased urinary excretion of lead began immediately after the injection of BAL, reached a peak in about two hours and then returned to the preinjection level in three or four hours. A preformed lead-BAL complex was injected into rabbits and found to be almost as toxic as lead acetate, despite the fact that it had a low dissociation constant. These authors concluded that BAL can release some lead from its combination with the tissues and force it to be excreted in the urine, but that the amount of lead thus eliminated is too small to effect the eventual outcome of the poisoning. In addition, they pointed out the possibility that a toxic lead-BAL complex could be formed in vivo, and postulated that this could account for the additive effects of BAL in experimental lead poisoning.

Chiodi and Sammartino[75] were able to increase the weight of rat kidneys by the daily administration of lead acetate. This increase in kidney weight did not appear when BAL was given concurrently with the lead acetate.

Human Poisoning

Telfer[76] studied the effect of BAL on a patient suspected of having lead poisoning. Although prior to BAL therapy the patient's urinary output of lead was within normal limits, the urinary lead excretion increased after therapy.

Ryder and his co-workers[77] studied the effects of a single intramuscular dose of BAL on the lead concentration in the blood and urine of men who had been exposed to lead. After BAL the concentration of lead in the whole blood started to fall within seven and a half minutes, reached a minimum in eight hours and returned to the original level in twenty-four hours. Simultaneously, there was an increase in the urinary output of lead. This effect could be produced repeatedly by subsequent injections of BAL. In spite of the reduction in the whole-blood lead concentration by BAL, the plasma levels were unaffected, indicating that large amounts of lead were released from the erythrocytes and rapidly removed from the blood stream. Although BAL produced these findings, which are of interest, it failed to shorten the clinical course of lead intoxication.

Cadmium

Cadmium is a sulfhydryl enzyme inhibitor, and its inhibitory effect can be reversed by BAL and other dithiols. The monothiol glutathione can bring about reactivation also, but only when given in large amounts.[56]

Lethal doses of cadmium given parenterally cause intense gastrointestinal activity, muscular weakness, prostration, severe dyspnea and death within twenty-four hours. Gilman and his co-workers[48] found that BAL could prevent this acute death from taking place in rabbits, if it were given just prior to the cadmium, but a delayed death from renal damage invariably occurred. Paradoxically, when BAL was given thirty minutes after a lethal dose of cadmium, only 50 per cent of the animals died, although, again, all deaths were the result of renal failure. More effective than BAL was BAL glucoside, which protected the majority of animals from the lethal effects of cadmium. Thiosorbitol and thioxylate, both monothiols, saved only a limited number of animals from cadmium deaths. Strangely enough, all the fatal results in the monothiol-treated animals were from typical acute cadmium poisoning rather than from renal damage as in animals dying after BAL and BAL glucoside therapy. The authors postulated that the renal deaths following BAL therapy could be explained by the assumption that BAL and cadmium form a relatively unstable complex. Hence, although BAL diverts the cadmium away from tissues usually affected by this metal, it carries it to the kidney, where enough cadmium dissociates to cause severe renal damage. The decrease in renal damage seen

when BAL is given thirty minutes after the administration of cadmium is explained by the supposition that some of the cadmium becomes irreversibly fixed in the tissues, and thus a smaller amount eventually reaches the kidneys.

The same authors found that, depending upon the pH of the solution, cadmium united with one or two moles of BAL to form two different complexes: Cd-BAL and Cd $(BAL)_2$. Cadmium also formed similar complexes with BAL glucoside, thiosorbitol, and thioxylate. Although the Cd-$(BAL)_2$ complex had a low dissociation constant in vitro, a readily available supply of cadmium ions seemed to be available when this complex was preformed and then injected into rabbits. Depending upon the amount given, the animals died either acutely from typical cadmium poisoning or several days later from renal impairment. Preformed Cd $(BAL\ glucoside)_2$ proved to be relatively nontoxic, probably because the complex is too large to be absorbed readily by the renal cells.

Both BAL and BAL glucoside were found to increase the excretion of cadmium from cadmium-poisoned animals. The BAL-treated animals showed an increase in both urinary and fecal cadmium, whereas those treated with BAL glucoside showed an increase in urinary cadmium only.[78]

In an extensive inhalation study in dogs and mice, it has been shown that cadmium mists can cause acute death from massive pulmonary edema, or delayed death from diffuse pneumonitis often associated with lung abscesses, anorexia, bloody diarrhea and generalized wasting. BAL prevented death in a number of animals when it was given one to three hours after the cadmium exposure. However, when BAL was given prior to the exposure to cadmium, it actually hastened death, presumably by fixing the cadmium in the lungs, where it could do the most damage.[79]

Silver

In a limited study, Olcott and Riker[80] found BAL ineffective against experimental argyria. They gave small daily doses of silver nitrate to 2 white rats for four hundred and fifty-six days. One animal was then given nine injections of BAL over a period of eighteen days. Autopsy and histologic examination showed no essential differences in the amounts of silver deposited in the two animals. The authors concluded that BAL would probably be of no value in the treatment of argyria in man.

Miscellaneous Metals

Antimony

Barron and Kalnitsky[56] reported that attempts to reactivate the succinoxidase enzyme system inhibited by antimony were unsuccessful with BAL, whereas glutathione was effective in reversing this inhibition. On the other hand, Thompson and Whittaker[55] found that BAL not only protected the brain pyruvate oxidase system from inhibition by antimony but also protected rats poisoned with this metal. Eagle and his co-workers[81] observed that BAL protected rabbits poisoned with various antimony compounds. An increase in antimony excretion in the urine persisting for two to four hours occurred after each injection of BAL. Similar results were obtained by Braun et al.[73]

Tellurium

Amdur[82] used BAL to treat 3 men who had inhaled tellurium-containing fumes and developed a characteristic garliclike odor of the breath. Although BAL failed to cause an increased urinary excretion of tellurium, the author believed that it was instrumental in decreasing the duration of halitosis from a possible period of weeks or months to a period of eleven to fourteen days in each case.

Copper, Bismuth, Chromium, Nickel, Zinc, Thallium, Selenium and Vanadium

McDonald[83] has reported that BAL glucoside in small doses caused an increased urinary copper excretion in normal sheep. The excretion reached a maximum of thirty times normal within an hour and then fell rapidly to a normal rate.

In enzyme-inhibition studies, Barron and Kalnitsky[56] found that BAL was effective against zinc, only partly effective against bismuth and totally ineffective against vanadium and selenium. Braun et al.,[73] in animal experiments, found BAL to be an effective antidote in poisoning from bismuth, chromium and nickel, but of no value against thallium and selenium. The administration of BAL actually hastened the death of animals poisoned with the latter metal.

Alloxan

Lazarow[84] reported that large doses of monothiols such as cysteine, glutathione and thioglycollic acid completely protected rats against a diabetogenic dose of alloxan. The dithiol BAL in smaller amounts was found to be equally effective in protecting the animals from alloxan. However, neither the dithiol nor the monothiols protected the animals unless given before or immediately after the administration of alloxan. It has been postulated that alloxan causes an immediate, irreversible change, which can be prevented only by the early use of sulfhydryl groups, and, in contrast to heavy-metal poisonings, this change cannot be reversed by dithiols.

Phenylthiourea

After the introduction of phenylthiourea and ANTU (alpha-naphthyl-thiourea) as powerful rodenticidal agents, a search has been made for suitable antidotes to be used in cases of accidental

poisonings. Harvey and his co-workers,[85] on the basis of the findings of Du Bois[86] that ANTU inhibits sulfhydryl-containing enzymes, investigated the value of BAL and 1-thiosorbitol in phenylthiourea poisoning. ANTU and phenylthiourea are similar in action, and the latter was used in this experiment because of its greater solubility in water. The authors found that 1-thiosorbitol given to rats immediately after the administration of phenylthiourea protected these animals from the toxic and lethal effects of phenylthiourea. On the other hand, BAL increased rather than decreased the toxic effects of phenylthiourea. This paradox of a monothiol affording protection from a substance while a dithiol increases the toxic effects of that substance is similar to a situation seen in cadmium poisoning in which thiosorbitol is effective but BAL fails and even potentiates the action of cadmium.

Dosage Schedules

Sufficient experience in the use of BAL has been accumulated to permit tentative recommendations concerning proper dosage schedules for the treatment of arsenic and mercury poisonings. However, too little clinical information is available, as yet, to justify the formation of specific dosage regimens for the use of BAL in other metal poisonings.

The Council on Pharmacy and Chemistry of the American Medical Association[87] suggests that BAL be given by intramuscular injection according to the following schedules:

For severe arsenic reactions, each injection to contain 3 mg. of BAL per kilogram of body weight.

First day Second day	6 injections per day, at the rate of one injection every four hours.
Third day	4 injections
Following ten days or until recovery	2 injections per day

For mild arsenic reactions, each injection to contain 2.5 mg. per kilogram.

First day Second day	4 injections per day
Third day	2 injections
Following ten days or until recovery	one injection per day

For mercury poisoning, larger doses of BAL are suggested. An initial dose of 5 mg. per kilogram of body weight should be given, to be followed in one to two hours by a dose of 2.5 mg. per kilogram. After two to four hours a second dose of 2.5 mg. should be administered, and in severe cases a third dose of 2.5 mg. should be given within the first twelve hours. On the second day, two doses of 2.5 mg. per kilogram should be used, and on the third day one dose of 2.5 mg. per kilogram is to be given.

Woody and Kometani[32] successfully treated 42 infants and children with BAL for arsenic poisoning. Children suspected of arsenic ingestion but without symptoms of arsenic poisoning were given three to six doses of 2.5 mg. per kilogram of body weight each at intervals of four to eight hours. Children with mild symptoms of arsenic poisoning were given six to twelve doses of 2.5 to 3.5 mg. per kilogram each at intervals of four to eight hours. Those with severe symptoms were given six to twelve doses of 3.5 to 5.0 mg. per kilogram each at intervals of four to eight hours.

Summary

BAL (2,3-dimercaptopropanol) was developed as an antidote against poisoning from the arsenic-containing war gas, lewisite. Since it is easily oxidized and unstable in aqueous solutions, BAL is commercially available only in a preparation containing peanut oil and benzyl benzoate, which is suitable for intramuscular administration alone. BAL is of value in the treatment of certain metal poisonings because it displaces the metal from its combination with the sulfhydryl groups of enzyme proteins with the formation of a metal-BAL complex, which is excreted. Although BAL in therapeutic doses may produce unpleasant side effects these are transient. BAL has been shown to be of clinical value in the treatment of arsenic, mercury and gold poisonings. Further clinical studies are necessary before the efficacy of BAL in other metal poisonings can be evaluated. Studies on animals suggest that BAL actually enhances the toxicity of certain metals. Therefore, BAL should not be used indiscriminately in the treatment of metal poisonings.

55 Shattuck Street

References

39. Stocken, L. A., and Thompson, R. H. S. British anti-lewisite: arsenic and thiol excretion in animals after treatment of lewisite burns. *Biochem. J.* **40**:548-554, 1946.

40. Harrison, H. E., et al. Treatment by 2,3-dimercaptopropanol (BAL) of systemic toxic effects of skin contamination with lewisite and phenyldichlorarsine. *J. Pharmacol. & Exper. Therap.* (Supp.) **87**:81-84, 1946.

41. Riker, W. F., Jr., and Rosenfield, G. Effect of 2,3-dimercaptopropanol on whole blood and plasma concentration of arsenic after mapharsen in cats. *J. Pharmacol. & Exper. Therap.* (Supp.) **87**: 72-75, 1946.

42. Peters, R. A., and Stocken, L. A. Preparation and pharmacological properties of 4-hydroxymethyl-2-(3'-amino-4'-hydroxyphenyl)-1:3-dithia-2-arsacyclopentane (mapharside-BAL compound). *Biochem. J.* **41**:53-56, 1947.

43. Gilman, A., Philips, F. S., Allen, R. P., and Koelle, E. S. Treatment of acute cadmium intoxication in rabbits with 2,3-dimercaptopropanol (BAL) and other mercaptans. *J. Pharmacol. & Exper. Therap* (Supp.) **87**:85-101, 1946.

44. Gilman, A., Allen, R. P., Philips, F. S., and St. John, E. Clinical uses of 2,3-dimercaptopropanol (BAL). X. Treatment of acute systemic mercury poisoning in experimental animals with BAL, thiosorbitol and BAL glucoside. *J. Clin. Investigation* **25**:549-556, 1946.

45. Koppanyi, T., and Sperling, F. Central and autonomic effects following combined administration of sodium arsenite and 2,3-dimercaptopropanol (BAL). *J. Pharmacol. & Exper. Therap.* **89**:350-355, 1947.

46. Kensler, C. J., Abels, J. C., and Rhoads, C. P. Arsine poisoning, mode of action and treatment. *J. Pharmacol. & Exper. Therap.* **88**:99-108, 1946.

47. Riker, W. F., Jr. Treatment of experimental arsenic poisoning with dithiols. *J. Pharmacol. & Exper. Therap.* (Supp.) **87**:66-71, 1946.

48. Levvy, G. A. Study of arsine poisoning. *Quart. J. Exper. Physiol.* **34**:47-67, 1947.

49. Hughes, W. F., Jr. Clinical uses of 2,3-dimercaptopropanol (BAL). IX. Treatment of lewisite burns of eye with BAL. *J. Clin. Investigation* **25**:541-548, 1946.

50. Carleton, A. B., et al. Clinical uses of 2,3-dimercaptopropanol (BAL). VI. Treatment of complications of arseno-therapy with BAL (British anti-lewisite), with appendix upon excretion of arsenic. *J. Clin. Investigation* **25**:497-527, 1946.

51. Longcope, W. T., Lentscher, J. A., Jr., Wintrobe M. M., and Jäger, V. Clinical uses of 2,3-dimercaptopropanol (BAL). VII. Treatment of arsenical dermatitis with preparations of BAL. *J. Clin. Investigation* **25**:528-533, 1946.

52. Holley, H. L. Use of BAL (2,3-dimercaptopropanol) in treatment of agranulocytosis following intensive arsenotherapy for syphilis. *Ann. Int. Med.* **27**:231-238, 1947.

53. Schrumpf, A. BAL therapy of thrombopenic purpura after arsphenamine treatment. *J. A. M. A.* **135**:1152, 1947.

54. Friedenberg, S. Tryparsamide optic neuritis treated by 2,3-dimercaptopropanol (BAL). *J. A. M. A.* **135**:1072, 1947.

55. Thompson, R. H. S., and Whittaker, V. P. Antidotal activity of British anti-lewisite against compounds of antimony, gold, and mercury. *Biochem. J.* **41**:342-346, 1947.

56. Barron, E. S. G., and Kalnitsky, G. Inhibition of succinoxidase by heavy metals and its reactivation with dithiols. *Biochem. J.* **41**: 346-351, 1947.

57. Stocken, L. A. British anti-lewisite as antidote for acute mercury poisoning. *Biochem. J.* **41**:358-360, 1947.

58. Longcope, W. T., and Luetscher, J. A., Jr. Clinical uses of 2,3-dimercaptopropanol (BAL). XI. Treatment of acute mercury poisoning by BAL. *J. Clin. Investigation* **25**:557-567, 1946.

59. Long, W. K., and Farah, A. Influence of certain sulfhydryl compounds on toxicity of organic mercurial diuretic. *J. Pharmacol. & Exper. Therap.* **88**:388-399, 1946.

60. Long, W. K., and Farah, A. Effect of some sulfhydryl-containing substances on toxicity of organic mercurial compound. *Science* **104**:220, 1946.

61. Sussman, R. M., and Schack, J. A. BAL inhibition of mercurial diuresis in congestive heart failure. *Proc. Soc. Exper. Biol. & Med.* **66**:247, 1947.

62. Maresh, G., Jr., and Farah, A. Effect of 2,3-dimercaptopropanol upon diuretic action of mersalyl. *Federation Proc.* **6** (*Part* II):354, 1947.

63. Earle, D. P., and Berliner, R. W. Effect of 2,3-dimercaptopropanol on diuresis. *Am. J. Physiol.* **151**:215:220, 1947.

64. Handley, C. A., and LaForge, M. Effect of thiols on mercurial diuresis. *Proc. Soc. Exper. Biol. & Med.* **65**:74, 1947.

65. Farah, A., and Maresh, G. Influence of sulfhydryl compounds on diuresis and renal and cardiac circulatory changes caused by mersalyl. *J. Pharmacol. & Exper. Therap.* **92**:73-82, 1948.

66. Lehman, R. A. Further studies on acute toxicity of mercurial diuretics. *Proc. Soc. Exper. Biol. & Med.* **64**:428-433, 1947.

67. Cohen, S. J. Pharmacology and toxicology of some new organomercury compounds. *J. Pharmacol. & Exper. Therap.* **35**:343-350, 1929.

68. Bivings, L., and Lewis, G. Acrodynia: new treatment with BAL. *J. Pediat.* **32**:63-65, 1948.

69. Ragan, C., and Boots, R. H. Treatment of gold dermatitis: use of BAL (2,3-dimercaptopropanol). *J. A. M. A.* **133**:752-754, 1947.

70. Cohen, A., Goldman, J., and Dubbs, A. W. Treatment of acute gold and arsenic poisoning: use of BAL (2,3-dimercaptopropanol, British anti-lewisite). *J. A. M. A.* **133**:749-752, 1947.

71. Margolis, H. M., and Caplan, P. S. BAL in treatment of toxicity from gold. *Ann. Int. Med.* **27**:353-360, 1947.

72. Lockie, L. M., Norcross, B. M., and George, C. W. Treatment of two reactions due to gold: response of thrombopenic purpura and granulocytopenia to BAL therapy. *J. A. M. A.* **133**:754, 1947.

73. Braun, H. A., Lusky, L. M., and Calvery, H. O. Efficacy of 2,3-dimercaptopropanol (BAL) in therapy of poisoning by compounds of antimony, bismuth, chromium, mercury and nickel. *J. Pharmacol. & Exper. Therap.* (Supp.) **87**:119-125, 1946.

74. Germuth, F. G., Jr., and Eagle, H. Efficacy of BAL (2,3-dimercaptopropanol) in treatment of experimental lead poisoning in rabbits. *J. Pharmacol. & Exper. Therap.* **92**:397-410, 1948.

75. Chiodi, H., and Sammartino, R. A. Nephrotoxic and renotropic effects of lead on white rats and its prevention by BAL. *Nature, London* **160**:680, 1947.

76. Telfer, J. G. Use of BAL in lead poisoning: preliminary report on one case. *J. A. M. A.* **135**:835-837, 1947.

77. Ryder, H. W., Cholak, J., and Kehoe, R. A. Influence of dithiopropanol (BAL) on human lead metabolism. *Science* **106**:63, 1947.

78. Tepperman, H. M. Effect of BAL and BAL-glucoside therapy on excretion and tissue distribution of injected cadmium. *J. Pharmacol. & Exper. Therap.* **89**:343-349, 1947.

79. Tobias, J. M., et al. Pathology and therapy with 2,3-dimercaptopropanol (BAL) of experimental Cd poisoning. *J. Pharmacol. & Exper. Therap.* (Supp.) **87**:102-118, 1946.

80. Olcott, C. T., and Riker, W F., Jr. Experimental argyrosis. II. Treatment of rats receiving silver with 2,3-dimercaptopropanol (BAL). *Science* **105**:67, 1947.

81. Eagle, H., Germuth, F. G., Magnuson, H. J., and Fleischman, R. Protective action of BAL in experimental antimony poisoning. *J. Pharmacol. & Exper. Therap.* **89**:196-204, 1947.

82. Amdur, M. L. Tellerium: accidental exposure and treatment with BAL in oil. *Occup. Med.* **3**:386-391, 1947.

83. McDonald, I. W. Effect of BAL-intrav on excretion of copper by sheep. *Nature, London* **157**:837, 1946.

84. Lazarow, A. Further studies of effect of sulphur compounds on production of diabetes with alloxan. *Proc. Soc. Exper. Biol. & Med.* **66**:4-7, 1947.

85. Harvey, T. S., Tatum, H. J., and Himmelfarb, S. L-thiosorbitol and BAL as antidotes in phenylthiourea poisoning. *J. Pharmacol. & Exper. Therap.* **90**:348-350, 1947.

86. Du Bois, K. P. Cited by Harvey, Tatum and Himmelfarb.[85]

87. Report of the Council on Pharmacy and Chemistry, of the American Medical Association. "BAL" (British anti-lewisite) in treatment of arsenic and mercury poisoning. *J. A. M. A.* **131**:824, 1946.

Additional References

Barron, E. S. G., et al. Reactivation by dithiols of enzymes inhibited by lewisite. *Biochem. J.* **41**:69-74, 1947.

Chance, A. C., and Levvy, G. A. Effects of BAL on excretion of arsenoxides. *Quart. J. Exper. Physiol.* **34**:79-82, 1947.

Eagle, H. Systemic treatment of arsenic poisoning with BAL (2,3-dimercaptopropanol). *J. Ven. Dis. Inform.* **27**:114-121, 1946.

Eagle, H. Recent studies in arsenical chemotherapy. *Tr. & Stud., Coll. Physicians, Philadelphia* **14**:49-54, 1946.

Editorial. Substance called BAL. *Brit. M. J.* **1**:240, 1946.

Editorial. BAL in oil for treatment of severe mapharsen reactions. *Bull. U. S. Army M. Dept.* **4**:327, 1945.

Gilman, A. Therapeutic applications of chemical warfare agents. *Federation Proc.* **5**:285-292, 1946.

Harrison, H. E., et al. Poisoning from inhalation of vapors of lewisite and phenyldichlorarsine: its pathology in dog and treatment with 2,3-dimercaptopropanol (BAL). *J. Pharmacol. & Exper. Therap.* (Supp.) **87**:76-80, 1946.

Krop, S. Action of 2,3-dimercaptopropanol (BAL) and related dithiols on isolated skeletal muscle of frog. *J. Pharmacol. & Exper. Therap.* (Supp.) **87**:60-65, 1946.

Luetscher, J. A., Eagle, H., and Longcope, W. T. Clinical uses of 2,3-dimercaptopropanol. VIII. Effect of BAL on excretion of arsenic in arsenical intoxication. *J. Clin. Investigation* **25**:534-540, 1946.

Report from the BAL Conference, Medical Research Council. British anti-lewisite: its use and therapeutic value in arsenical intoxications. *Lancet* **2**:497, 1947.

Stocken, L. A., Thompson, R. H. S., and Whittaker, V. P. British anti-lewisite: antidotal effects against therapeutic arsenicals. *Biochem. J.* **41**:47-52, 1947.

Sulzberger, M. B., and Baer, R. L. Development and use of BAL: review, with particular reference to arsenical dermatitis. *J. A. M. A.* **133**:293-296, 1947.

Thompson, J. F., Savit, J., and Goldwasser, E. Tests of 2,3-dimercaptopropanol (BAL) and related dithiols for decontamination of lewisite on human skin. *J. Pharmacol. & Exper. Therap.* **89**:1-13, 1947.

Whittaker, V. P. Experimental investigation of "ring hypothesis" of arsenical toxicity. *Biochem. J.* **41**:56-62, 1947.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 34531

PRESENTATION OF CASE

A sixty-one-year-old man was admitted to the hospital because of vomiting and diarrhea of one year's duration.

The diarrhea, which was described as occurring five or six times daily, was watery, brownish and without gross evidence of blood. The vomiting occurred once or twice a week, usually at night after retiring. It was accompanied by moderate epigastric fullness and dull substernal discomfort, which were not apparently related to food ingestion. In the six months before admission frequency of the attacks of vomiting increased to almost every night. At this time the patient noted the onset of burning and rolling sensations in the pit of the stomach. These symptoms were relieved somewhat by the emesis, which was liquid and mucoid in character. Anorexia was very marked. There was no postprandial distress, pain between meals, tarry stools or jaundice. He had lost 70 pounds since the onset of illness.

The past history revealed rheumatoid arthritis since the age of thirty years, when he had a severe attack with involvement of almost every joint. A bilateral knee-joint reconstruction was done after the acute stage. At this time he experienced the onset of mild exertional dyspnea and dependent edema. In spite of this he was alleged to have been in good general health but was unable to work because of the arthritis.

Physical examination revealed an extremely cachectic man in no acute distress. The chest was emphysematous, with limited expansion. There were moist, sibilant rales in the left axilla and at both bases. The heart was not enlarged. The liver edge was palpated four fingerbreadths below the costal margin. The spleen was not felt. A large, reducible, supraumbilical, ventral hernia was present. Marked arthritic changes involving almost every joint, with limitation of movements, were observed. These appeared to be in a quiescent stage.

The temperature was 99°F., the pulse 80, and the respirations 20. The blood pressure was 120 systolic, 80 diastolic.

Examination of the blood showed a red-cell count of 5,300,000, with a hemoglobin of 12 gm., and a white-cell count of 21,300, with 70 per cent neutrophils. The urine had a specific gravity of 1.014 and contained no albumin. Subsequent specimens gave +++ to ++++ tests for albumin. There were a few white cells in the sediment. The nonprotein nitrogen was 50 mg., and the total protein 7.75 gm. per 100 cc., with an albumin of 3 gm. and a globulin of 4.75 gm. The chloride was 108 milliequiv. per liter, and the alkaline phosphatase 6.6 units. The prothrombin time was 17 seconds (normal, 16 seconds), the cephalin flocculation test was ++ at twenty-four hours and +++ at forty-eight hours, and the bromsulfalein test showed 10 per cent retention of the dye. A Congo-red test revealed a 52 per cent retention of dye in the serum.

X-ray studies of the gastrointestinal tract gave findings suggestive of pyloric obstruction, with marked pylorospasm. A barium enema was negative. A chest film showed extensive fibrotic emphysematous and bronchiectatic changes in both lungs. An electrocardiographic record was within normal limits. The gastric fluid on analysis revealed high acidity and was guaiac negative. Cytologic study of smears was reported negative. The stools were guaiac negative. After admission repeated gastric aspirations of 150 to 300 cc. resulted in some decrease of the vomiting, but the patient continued complaining of gastric fullness.

On the eighth hospital day a partial gastrectomy and repair of the ventral hernia were performed. Following operation he noted no relief of the gastric fullness and complained of increasing pain and stiffness of joints. The nonprotein nitrogen began to rise, from 50 mg. to 72 to 170 mg., finally reaching 225 mg. per 100 cc., with a fall of the chloride to 78 milliequiv. per liter and of the total protein to 5.4 gm. per 100 cc. The watery diarrhea recurred, and marked dyspnea and cyanosis developed. Moist rales were heard almost to the top of both lungs. On the twenty-second hospital day he became unresponsive and died.

DIFFERENTIAL DIAGNOSIS

DR. BERNARD M. JACOBSON: Can you tell us the figures on the acidity of the gastric fluid?

DR. TRACY B. MALLORY: A fasting specimen was reported as 50 units of free and 80 units of combined acid.

DR. JACOBSON: A considerable degree of acidity.

As I read over this patient's history and before I got to the report of the x-ray examination, a number of thoughts occurred to me about the fundamental diagnosis. Apparently for a considerable period of time there was a watery, brownish diarrhea without gross evidence of blood but with associated cramps in the lower abdomen. The diarrhea seemed more prominent than the vomiting, which occurred only once or twice a week, usually after retiring. The

possibilities that ran through my mind as causes of long-continued diarrhea without pus or blood or tenesmus include a few common conditions and a few unusual conditions that might be mentioned. Against such a condition as ulcerative colitis or regional ileitis was the lack of blood, pus or tenesmus. The presence of a carcinomatous lesion anywhere in the gastrointestinal tract from the stomach downward should certainly be considered. The question of a fistula between various segments of the gastrointestinal tract must be considered, and that could account for this type of diarrhea. The possibilities outside the gastrointestinal tract — general and systemic disease that can cause this type of diarrhea — come to mind. Chronic uremia is one of the commonest. Chronic nitrogen retention can be associated with this type of diarrhea and last many months. One thinks of such diseases as Addison's disease as causing diarrhea and vomiting and also of pernicious anemia and sprue, but the subsequent physical and laboratory findings give no evidence for either Addison's disease, pernicious anemia or sprue, nor is there any evidence later on that suggests hyperthyroidism as the cause of that type of diarrhea. As one goes along a little bit in the history, one finds that when the vomiting became more pronounced, beginning to occur almost daily, the material vomited was liquid and mucoid. I presume we would know from the patient whether the liquid was heavily stained with bile because that is usually mentioned at some time in a patient's history. In the absence of small-bowel content of the vomitus I think we must assume that there was obstruction at the pylorus. This was not low intestinal obstruction. The amount of vomiting, it seems to me, is out of proportion to what we may expect as secondary to some of the systemic diseases I have mentioned.

On physical examination the liver edge was four fingerbreadths below the costal margin. In view of the obvious emphysema I assume the upper border was quite low and the liver was not large but merely ptotic. I am rather surprised we were not told about the examiner's feeling a mass in the abdomen, especially in the presence of the hernia. Perhaps I should not expect to feel a mass, but I think I do.

As far as the laboratory work goes, there are a few items of interest. A mild hypochromic anemia was present. We are told that one urine on admission had a specific gravity of 1.014; probably the patient did not have a specific-gravity concentration test, but it would be of some interest to know if he could concentrate. Most of the urine apparently contained a huge amount of albumin and a few pus cells. I would be interested to know if the patient had an intravenous phenolsulfonephthalein test, since we see later that kidney failure played an important part in the patient's terminal career.

DR. MALLORY: There was a phenolsulfonephthalein excretion of 0 in fifteen minutes, 5 per cent in sixty and 5 per cent in twelve.

DR. JACOBSON: What volume?

DR. MALLORY: No volume was recorded.

DR. JACOBSON: Assuming that the urinary volume was fairly good, this obviously indicates impairment in renal function — no excretion in fifteen minutes.

DR. MALLORY: No concentration test is recorded but subsequent specific gravities are 1.005, 1.003, 1.010 and 1.006.

DR. JACOBSON: Reversal of the albumin-globulin ratio is of some interest, suggesting systemic disease with increasing serum globulin. There is no good evidence of any one disease. Some degenerative disease of the liver might have caused this high serum globulin. Rheumatoid arthritis can sometimes cause high serum globulin. I doubt if that would be suggestive of multiple myeloma or sarcoid or some of the other conditions. I suspect that the globulin may be elevated due to rheumatoid arthritis. The amount of liver-function defect, as measured by the cephalin flocculation and bromsulfalein test, is of no great significance in a person as malnourished as this. Later we note the low serum chloride, which was initially rather high, perhaps because of dehydration. The phosphatase of 6.6 units is against biliary obstruction. The normal prothrombin time is also against marked derangement of liver function.

DR. STANLEY M. WYMAN: The films of the chest show a diffuse linear process throughout both lung fields extending from the hili. There are suggestions of dilated bronchi in the periphery of the right-upper-lung field. The hilar shadows are prominent, but I can see no definite lymph nodes or other masses. The heart shadow is not remarkable for a man of this age. The chest is increased in the anteroposterior diameter, and I think the whole picture is quite consistent with fibrosis and emphysema, although of course lymphatic metastases cannot be entirely excluded. The films of one barium-enema examination show an intrinsically normal-appearing colon, with a loop of barium-filled bowel, I think probably ileum, extending out into the hernial sac and other gas-filled loops of bowel, which are probably ileum in the sac. The hepatic flexure is displaced downward, and the upper margin of the liver extends reasonably high, which makes me wonder about increase in the size of the liver from this examination.

The next films are of the gastrointestinal examination done on at least two occasions. I am sure the examiner had a great deal of difficulty with this patient because of the arthritis. I think the important thing on these films is that there is a large, soft-tissue shadow in the right upper quadrant that I believe displaced the duodenum and stomach to the left, and, as one can see in this projection, this lies somewhat anteriorly. Apparently, the examiner had a great deal of difficulty in obtaining good visualization of the pylorus and the distal duodenum, and we have no film with good filling of the distal duodenum. The few traces that we have of barium in the duodenum show a suggestion of some irregularity

in the mucosal pattern. There is a suggestion of some radiolucency overlying the liver. This, again, is not a definite finding. The film that might have shown it best is of unsatisfactory quality. There is one, and only one, spot film that shows an unusual accumulation of barium at this point, which makes one wonder about barium in the common duct. I would say that the liver was enlarged and displaced the stomach. It may be that the second portion of the duodenum is narrowed. I cannot comment intelligently on the pylorus. The changes may be due to extrinsic pressure.

DR. JACOBSON: Dr. Wyman has pointed out that the upper portion of the liver was not low as I suspected and that the stomach was apparently pushed to the left. In that case we must believe the liver was large and was the seat of disease.

The Congo-red test, which showed 52 per cent retention, apparently a doubtful borderline finding, gave no definite evidence of systemic amyloid disease. There are certain forms of amyloid disease — the atypical type that might infiltrate the walls of the small bowel — that will not take up Congo-red dye. We cannot see any visualization of the small bowel — no leakage of barium directly into the colon.

DR. WYMAN: I should not say so.

DR. JACOBSON: If we could have a picture of the upper small bowel, it would be helpful.

DR. WYMAN: This is the closest we came to it. I would consider these jejunal folds to be within normal limits.

DR. JACOBSON: Was an intravenous pyelogram done?

DR. WYMAN: No.

DR. JACOBSON: I rather suspect that the correct diagnosis was not well understood preoperatively and that some of the reasoning that I have gone through was also discussed by the clinicians on the service before operation. This patient obviously had pyloric obstruction. We must assume vomiting secondary to pyloric obstruction and not systemic disease.

What of the diarrhea? We have no evidence of intrinsic small-bowel or large-bowel disease. Can we tie up the vomiting and the diarrhea into one diagnosis? It is possible if we assume that the patient had carcinoma of the pylorus. Many patients with carcinoma of the stomach have diarrhea, the exact mechanism of which we do not know. The evidence for carcinoma of the stomach in this patient is the progressive downhill course. The history of the type of discomfort he had in the stomach is perfectly consistent with it. For the diagnosis of pyloric obstruction due to ulcer there may be more evidence from the laboratory point of view — high gastric acidity and the negative cytologic smear. The lack, however, of a good, clear history of postprandial pain typical of ulcer stands out, and the combination of pyloric obstruction and diarrhea inclines me a little more to the diagnosis of carcinoma rather than ulcer. Some few cases of carcinoma do have high gastric acidity. I cannot visualize any other specific cause for diarrhea.

What happened after operation is certainly an interesting phenomenon. The kidney failure, which may have been very minimal before operation, set in quite promptly. The patient obviously died in uremia. Terminally he had left-sided heart failure and pulmonary edema.

I believe that in recent years major surgery in patients with cardiac disease has become less and less of a risk and that the experience of many surgeons and physicians is that renal failure is probably a most important postoperative condition.

What was the renal failure due to? We have no good evidence that this patient had chronic glomerulonephritis or chronic vascular nephritis, although it may well be that the initial blood pressure of 120 systolic, 80 diastolic, reflected a man with some degree of heart failure, with lowered blood pressure. Against increased hypertension is the fact that the heart shadow was normal.

Could this have been pyelonephritis? It certainly could. At these sessions Dr. Mallory has pointed out to many of us how often we miss the diagnosis of chronic pyelonephritis. The diagnosis is not too easy to make. The findings in the urinary sediment when the patient comes to the hospital may be minimal, and the blood pressure elevated or normal; all forms of kidney-function tests, of course, are markedly abnormal.

Could this have been an acute renal failure due to lower-nephron defect? We have no history of the patient's having received sulfonamides or incompatible transfusion. I shall assume that they were not given, and the possibility can be discarded.

I should like to conclude with a diagnosis of carcinoma of the pylorus, diarrhea secondary to the carcinoma, chronic pyelonephritis, terminal uremia, rheumatoid arthritis, bronchiectasis and terminal heart failure.

DR. F. DENNETTE ADAMS: I am worried about Dr. Jacobson's statement that he attributed the lower border of the liver and low diaphragm to emphysema. I doubt if it could happen. I do not believe I have seen it due to that, but I may be wrong. It seems to me that a low diaphragm due to emphysema would not have enough pressure to push the liver down.

I would like to ask if perhaps amyloid disease would explain the terminal picture, especially in a man with arthritis for so many years.

DR. JACOBSON: I think I have seen a low liver — that is, a ptotic liver — pushed down by the diaphragm, even without pulmonary emphysema. In view of the demonstration of the soft-tissue mass by Dr. Wyman, I am more suspicious that the liver was the seat of carcinomatous metastases.

Against amyloid disease, I do not believe the rheumatoid arthritis was active enough to produce that

much amyloid disease. The Congo-red test was not conclusive, nor was there enough bronchiectasis in the history to suggest amyloid disease secondary to that.

DR. JOHN B. STANBURY: I was much impressed by one interesting physical finding. You could pass your hand through the ventral hernia and outline a firm, smooth liver as I have never been able to do before — just as well as Dr. Mallory could examine it at postmortem examination.

The thing that puzzled us was why after operation the patient suddenly went into renal failure. He had borderline failure before operation. He had pyloric obstruction preceding operation. We took the risk. It did not work. He went quickly into renal failure, developed uremia, pulmonary edema and low chloride, went into pulmonary edema and heart failure and died. We gave him no sulfonamide.

DR. JACOBSON: No mass was felt in the abdomen through the hernia?

DR. STANBURY: No, just the liver.

CLINICAL DIAGNOSIS

Amyloid nephropathy, with uremia.

DR. JACOBSON'S DIAGNOSES

Carcinoma of pylorus.
Chronic pyelonephritis.
Terminal uremia.
Rheumatoid arthritis.
Bronchiectasis.
Terminal heart failure.

ANATOMICAL DIAGNOSES

Rheumatoid arthritis, chronic.
Amyloidosis of liver, spleen, kidneys and adrenal glands.
Bronchiectasis.
Bronchopneumonia.
Hypertrophy of heart.
Pericarditis, acute fibrinous, probably uremic.
Operative wound: resection of pylorus for obstruction.

PATHOLOGICAL DISCUSSION

DR. MALLORY: Autopsy showed that several of the organs were larger than the x-ray examinations indicated. The heart weighed over 500 gm., and the liver 3500 gm. — double the normal size. The spleen weighed 500 gm., and both kidneys 450 gm. We found that the liver, spleen and kidneys showed very extensive amyloid disease and there was also some involvement of the adrenal glands. There was extensive bronchiectasis, a terminal bronchopneumonia and an acute pericarditis. The stomach, which had been resected, was a great disappointment to the pathologists. We could find nothing wrong with it. At the time of operation a biopsy on which a frozen section was done showed only normal, smooth muscle, and the resected specimen only questionable hypertrophy of the muscle of the pyloric ring and perfectly normal mucosa — neither tumor nor ulcer. Localized amyloid tumors of the gastrointestinal tract do occur, and in the face of extensive amyloid disease we thought we might find amyloid in the pyloric ring, but there was none whatever.

DR. EDWARD B. D. NEUHAUSER: Why was a gastrectomy done?

DR. STANBURY: There seemed to be no question that the patient had functional pyloric obstruction. Perhaps a surgeon can answer that.

DR. W. R. RICHARDSON: I am sorry that Dr. John McKittrick is not here. I assisted at the operation and shall try to explain our findings and the choice of procedure.

A gastrotomy was done, and the pylorus and pyloric antrum visualized. There was a definite organic obstruction at the pylorus, an annular thickening that was submucosal with no ulceration. It narrowed the lumen to a diameter of less than 1 cm. and did not permit the passage of more than the distal portion of a hemostat. This band was broken down during the digital examination, with several linear mucosal tears resulting. Much of the band was removed submucosally and sent for frozen-section diagnosis, which revealed no evidence of a malignant lesion and was eventually noted as "hypertrophy of the pylorus."

Subtotal gastrectomy was performed because it was considered inadvisable to leave traumatized areas. That this was probably an unfortunate choice is now clear, and we would have felt much better had a gastroenterostomy or even a pyloroplasty been carried out, accepting whatever hazard there might have been in leaving the traumatized pylorus and pyloric antrum.

DR. MALLORY: One cause of pyloric obstruction seen from time to time in adults is ectopic pancreatic tissue in the pyloric sphincter. We looked carefully for that but were unable to find it. I think we must assume that the pyloric obstruction was functional. I have no doubt it was real.

DR. JACOBSON: Would Dr. Ropes comment on the significance of the Congo-red test?

DR. MARIAN ROPES: I think we have now seen enough cases corroborated at autopsy to say that this figure may mean amyloid disease. We still do not know what the percentages mean, but half our patients with rheumatoid arthritis show levels between 50 and 65 per cent and several have shown amyloid disease at autopsy. In addition, 15 per cent have positive levels — less than 50 per cent left in the serum. It is interesting also that the Congo-red retention does not seem to correspond with the severity of the arthritis or with the duration. We

have seen it in varying degrees of severity of arthritis.

DR. MALLORY: The amyloid deposits stained beautifully with Congo red at autopsy. It was the type that should have absorbed dye, I should think.

CASE 34532

PRESENTATION OF CASE

A forty-nine-year-old photographer entered the hospital complaining of dyspnea relieved by belching.

Five months before admission he experienced an episode of nausea, weakness and pain in the left arm, which was relieved by induced vomiting. He remained in bed for three days, and at this time a chest x-ray film showed an enlarged heart. He continued his usual activities but three months later awoke one night with sudden dyspnea, relieved by sitting on the edge of the bed for a few minutes. Since that time he had noticed gradually increasing dyspnea on exertion and frequent episodes of epigastric distress following meals, often associated with dyspnea.

Ten days prior to admission he noticed swelling of the ankles, which increased subsequently. During the past few months he had lost about 15 pounds.

Physical examination revealed a well developed, quiet man in no distress. The cardiac border was percussed 11 cm. to the left of the midline. There was a questionable diastolic gallop. The liver edge was palpated four fingerbreadths below the costal margin and was slightly tender. There was ++ edema of the ankles, extending up to the sacrum.

The temperature was 99.4°F., the pulse 90, and the respirations 24. The blood pressure was 115 systolic, 90 diastolic.

Examination of the blood revealed a hemoglobin of 14 gm., and a white-cell count of 12,000, with 77 per cent neutrophils, 19 per cent lymphocytes and 4 per cent monocytes. The urine had a specific gravity of 1.026 and gave a +++ test for albumin. Microscopical examination of the sediment showed rare red cells and 5 to 8 white cells per high-power field.

On the day following admission he experienced sudden pain in the right upper chest with a little sputum. Later a friction rub was heard on the right side, and a few rales at the right back. An x-ray film disclosed an area of somewhat mottled density lying in the anterior segment of the right upper lobe with its base against the pleura. There was a moderate quantity of fluid in the right pleural space. The lung fields otherwise appeared essentially clear except for some atelectasis in the right-lower-lung field medially. The heart shadow was enlarged to the right and left with a cardiothoracic ratio of 18:31.5; it was without characteristic configuration, and the pulsations were diminished in amplitude. Plain films of the abdomen showed the tip of the liver to lie unusually low, suggesting some enlargement of the liver. There was a hazy density obscuring some of the visceral shadows and raising the question of fluid in the abdomen. An electrocardiogram showed a normal rhythm, with a rate of 100, and a PR interval of 0.14; the T waves were inverted in Lead 1 and low in Leads 2 and 3, and there was a well marked left-axis deviation and an inverted T wave in Lead AVL with a small Q wave. The chest leads showed an upright T wave in Leads V-2 and V-4 and a flat T wave in V-5.

On the day following the episode of chest pain a bilateral superficial femoral-vein ligation was performed, and dicumarol and digitoxin were started. Tenderness of the right calf was noted on the next day. The patient continued to experience some dyspnea and occasionally raised some blood-streaked sputum. He began to run a temperature of about 100°F., and the rales at the right base persisted. The prothrombin activity became as low as 24 per cent, and digitoxin was stopped because he complained of nausea. An x-ray film on the seventh day again demonstrated the area of increased density within the anterior portion of the right upper lobe. This had increased in size since the previous examination. The right leaf of the diaphragm was considerably elevated. Very little, if any, fluid was made out. The left lung was clear. The heart was again observed to be markedly enlarged.

He continued to be nauseated and occasionally raised more bloody sputum. He developed a prominent gallop rhythm with occasional extrasystoles and dropped beats. He continued to fail slowly and developed pleural pain over the left chest posteriorly, with a loud friction rub. On the tenth hospital day he had a sudden episode of dyspnea and became increasingly cyanotic, with increase in pulse rate and lowering of blood pressure. Following this he was described as in a "chronic shocky state," and died on the following day.

DIFFERENTIAL DIAGNOSIS

DR. GORDON S. MYERS: May we see the x-ray films?

DR. STANLEY M. WYMAN: Unfortunately, we were unable to find any but these two portable films of the chest. They show the area of rather homogeneous density in the right-lung field, which appears to lie against the pleura of the anterior chest wall. There is some fluid in the fissure between the middle and lower lobes and the upper and lower lobes. The right lower lobe is decreased in size, and there is some density posteriorly, suggesting possibly another infarct. However, this film is of insufficient quality to warrant a definite conclusion. The heart shadow cannot be delineated, but it is a large heart, I believe, and is prominent in the region of the left ventricle. The left lung on these films appears clear.

DR. MYERS: Do you think the density here in the lower portion of the lobe as seen posteriorly can be consistent with pulmonary infarction?

DR. WYMAN: Yes, with some pleural fluid.

DR. BENJAMIN CASTLEMAN: This last set of films was taken on the tenth day, six days before the patient died.

DR. MYERS: I would like to begin by saying what I think the diagnosis may be and then try to explain my reasoning. I believe this man most likely had coronary-artery disease and the onset of the acute illness began with myocardial infarction, although we have no proof of that. I believe also that he had congestive failure and recurrent pulmonary emboli, both prior to and probably following treatment by superficial vein ligation and dicumarol.

The chief complaint was that of dyspnea, relieved by belching. That is an unusual chief complaint, but I suppose it is a valid one. If he had congestive failure with limitation of vital capacity and gaseous distention of the abdomen, the elevation of the diaphragm may have been responsible for some additional dyspnea, since we believe that dyspnea is proportional to ventilation divided by vital capacity.

Five months before admission this man had a curious episode of nausea, weakness and pain in the left arm, relieved by induced vomiting. That in itself is a nonspecific history. One would think, first of all, that he had something going on in the gastrointestinal tract. In view of the fact that later on we find that he had lost weight, despite the fact that he was becoming edematous, one might consider the possibility of carcinoma or some other serious lesion in the gastrointestinal tract. This history does not suggest pulmonary infarction or embolus at that time. The fact that he had pain in the left arm, even without chest pain, and that he had symptoms of indigestion certainly is consistent with the occurrence of myocardial infarction. We know that myocardial infarcts sometime occur without any symptoms. He remained in bed three days at this time. He had chest x-ray films, which showed an enlarged heart. If he had a myocardial infarct at this time, it might explain the fact that the heart appeared to be large on x-ray study and that he went on to symptoms suggesting left-sided heart failure. Thus, we can justifiably suspect myocardial infarct, but we cannot make a definite diagnosis of it from the facts at hand.

I think that the diagnosis of coronary-artery disease in a man forty-nine years old who showed congestive failure but no heart murmurs is the best bet. It is very unlikely that he had one of the rarer kinds of heart disease such as those following sulfonamide therapy and virus infection. We know that he had an episode of orthopnea. He woke up short of breath and was relieved by sitting on the edge of the bed. He had clear-cut dyspnea on exertion and also epigastric distress following meals, associated with dyspnea. If he had coronary-artery disease the symptoms of indigestion were not unusual since we know various functional gastrointestinal diseases are commonly associated with coronary disease — for example, cardiospasm, which gives symptoms of indigestion apart from the heart trouble. He may have had dyspnea after meals, partly because of abdominal distention and also because the work of the heart is increased after a full meal.

Ten days prior to admission he noted swelling of the ankles, which had increased. Despite this, he had a 15-pound weight loss, and one wonders if he had some kind of cachectic disease. I do not believe we can skip over that weight loss too lightly. However, he may have been afraid to eat, simply because eating aggravated his symptoms. Later on there is no clear-cut evidence of wasting disease such as thyrotoxicosis, cancer, diabetes or the like.

The physical examination, as stated, is consistent with congestive heart failure: there was a large heart, rapid pulse, a questionable diastolic gallop and so forth. The protocol states that the blood pressure was 115 systolic, 90 diastolic. It would be helpful to know if he had had any previous hypertension, whether or not there was venous distention, and also about the loudness of the pulmonic second sound, to get some idea whether there was pulmonary hypertension associated with left-sided heart failure.

DR. CASTLEMAN: The record states that there was distention and pulsation of the neck veins for 5 cm. above the clavicle.

DR. MYERS: That is additional evidence in favor of congestive failure. It certainly fits in with the rest of the picture.

Examination of the blood showed no definite anemia, a little increase in white-cell count and no real increase in neutrophils or lymphocytes. The urinary findings are consistent with the presence of congestive failure.

On the day following admission the patient experienced sudden pain in the right upper chest, with cough productive of a little sputum, and later a friction rub and a few rales were noted. This episode and the x-ray findings seem to be consistent with the presence of pulmonary infarction, although the small amount of fluid in the right pleural space could have been due either to congestive failure or to a pulmonary infarct that happened to be on the right side. The x-ray report states that there was atelectasis in the right-lower-lung field, but I believe that is a not uncommon statement in cases of small pulmonary infarcts. There may or may not have been additional atelectasis. The heart was large, without any special configuration, perhaps prominent in the region of the left ventricle. The cardiac pulsations were diminished. I do not believe that fact to be too helpful. Diminished pulsations may be due to the presence of pericardial fluid or simply to an enlarged, failing heart. There is certainly no evidence of constrictive pericarditis in the x-ray films or in the rest of the data that we have. The plain films of the abdomen, which we do not have here, were consistent with the presence of fluid and an enlarged liver, which were probably due to congestive heart failure.

We then come to the electrocardiograms. I am glad to have been able to see the tracings myself just now because they look a little more markedly deformed than one gathers from the description in the protocol. I am struck with the fact that there is a tendency to low voltage in the QRS complexes in the limb leads, and small R waves all across the chest, with an M-shaped QRS wave in V-5. The rest of the tracing is as stated in the protocol. The electrocardiogram is certainly not diagnostic. If one takes electrocardiograms of a large number of patients with pulmonary emboli, only about 10 per cent show characteristic findings of acute cor pulmonale. Thus, we need not be surprised when the electrocardiogram does not give us the diagnosis even if the patient had, as I assume he did, pulmonary infarcts.

How about the question of myocardial infarction? Certainly this electrocardiogram per se is not diagnostic of either old or recent myocardial infarction; however, it is consistent with coronary-artery disease, as well as with other diseases, which I do not believe we need go into because there is no other evidence in favor of them. How can the electrocardiogram be so nonspecific in acute myocardial infarction? In the first place, electrocardiograms may occasionally actually revert to normal a few months after the occurrence of a myocardial infarct. The initial episode here was five months before admission. In the second place, the localization of the myocardial infarct may be such that the standard procedure for placing the electrodes in a routine electrocardiogram fails to show the infarction even though present. The electrocardiogram may thus be normal unless special efforts are made to explore the chest thoroughly or unless an esophageal lead is taken. Third, and most important, is that serial electrocardiograms very frequently help to make the diagnosis of myocardial infarction by showing specific changes in pattern where a single tracing is of no help. Apparently, only one electrocardiogram was taken in this case. We can summarize the electrocardiographic findings by saying that although they are not diagnostic they certainly do not rule out an old anterior infarction. They are, in any case, consistent with the presence of coronary-artery disease. They do not show the typical changes of acute cor pulmonale, but we cannot be surprised at this, even in the presence of multiple pulmonary infarcts.

Following the initial episode in the hospital a superficial femoral-vein ligation was done and dicumarol given. We know that superficial femoral-vein ligations are occasionally followed by repeated pulmonary emboli, which also occur after treatment with dicumarol. It is true that superficial femoral-vein ligation is rarely followed by fatal pulmonary emboli; the same reservation holds for adequate treatment with dicumarol. The statement is made that the prothrombin level went as low as 24 per cent. That is not the important point. The point is whether over the period of treatment it had regularly been kept at a low level, somewhere between 10 and 30 per cent. If the prothrombin percentage gets down to 24 and a few days later it is up to 100, obviously we have inadequate protection for the patient. I think that the remainder of the story here is consistent with pulmonary infarcts despite the therapy that was carried out. The patient developed some cardiac arrhythmia. That may have been stimulated by the pulmonary emboli added to the presence of coronary-artery disease. The last episode before death, I believe, was more likely to have been a pulmonary embolism than myocardial infarction, although the latter is possible.

In summary, then, I believe that this patient had coronary-artery disease, with congestive failure. I believe there is a good possibility, although no proof, that he had myocardial infarction. I still think that the later episodes were pulmonary infarcts despite the dicumarol therapy and venous ligation.

DR. WYMAN: It is an unusual story for a pulmonary infarct to increase in size during the course of seven days. We are given the information that it lies against the pleural surface, but that is not entirely clear-cut from this film. I think an additional possibility that one might worry about is tumor of the lungs. I cannot exclude it from this examination.

DR. MYERS: I am grateful for your suggestion. Certainly, if there was some enlarging process in the lung atypical of pulmonary infarction, a tumor might help to explain the troublesome fact of marked weight loss in a case in which otherwise there is no definite explanation for it. I suppose the tumor, if present, could have been primary in the lung or possibly metastatic from somewhere under the diaphragm. In the latter case, it might explain the gastrointestinal symptoms that the patient had.

DR. JOHN B. QUINBY: What would be the source of the pulmonary emboli?

DR. MYERS: I suppose from the figures available one could bet, on a 75 per cent chance, from the legs and a 25 per cent chance from the heart chambers — in which case the emboli would arise from a mural thrombus.

DR. QUINBY: Even with ligation?

DR. MYERS: Yes. Only the superficial femoral-vein ligation was performed, the profunda was not included; and also there is the possibility of clots in the iliac vessels and higher up in the pelvis.

A PHYSICIAN: In how many cases of myocardial infarction have you seen the electrocardiogram return to normal?

DR. MYERS: I do not know exactly how many do.

A PHYSICIAN: It certainly does occur occasionally, but how many have you seen?

DR. MYERS: I cannot answer that. Dr. White[1] has some excellent illustrations in his book showing the return of electrocardiograms to normal following myocardial infarctions.

Clinical Diagnoses

Arteriosclerotic heart disease.
Coronary thrombosis, with myocardial infarction.
Phlebothrombosis of leg, with pulmonary embolism and infarction.

Dr. Myers's Diagnoses

Coronary-artery disease, congestive heart failure, probable myocardial infarction.
Multiple pulmonary infarcts.

Anatomical Diagnoses

Coronary thrombosis, with myocardial infarction.
Mural thrombi, left ventricle and both auricles.
Pulmonary infarcts, multiple, massive.
Coronary sclerosis, severe.
Cardiac hypertrophy.
Hydrothorax, bilateral.
Central congestion of liver.
Renal infarct.

Pathological Discussion

Dr. Castleman: Autopsy showed an enlarged heart, which weighed 500 gm. The coronary arteries were very severely sclerotic. The left had a pinpoint lumen throughout, and the right was also narrowed but, in addition, contained a recently organized thrombus. The anterior portion of the left ventricle was completely infarcted. The infarction involved the interventricular septum and extended through to involve the right portion of the septum, which is a relatively rare occurrence. There was a large mural thrombus over the infarct on the left side, but none on the right. A piece of this thrombus had apparently broken off and had produced an infarct to one of the kidneys, which may perhaps account for the red cells that were found in the urine. There were mural thrombi also in both auricles so that the emboli in the lungs could be accounted for by the right auricular thrombus. The lungs were the site of numerous infarcts and very large ones, much larger than we usually see. The infarct in the right upper lobe measured 7 cm. in diameter. The increase in size of the x-ray shadow between the two sets of films was due to an infarct in the right middle lobe that occurred later, and its shadow was superimposed upon that of the upper-lobe lesion. Some years ago Dr. Hampton[2] showed that increase in size and changes in shape of infarcts may be due to other infarcts occurring close by, and that was true in the case under discussion. In addition, the entire upper portion or dorsal division of the right lower lobe and almost the entire left lower lobe were infarcted. These probably occurred after ligation, since they appeared to be redder and more recent than the others. I have the impression, and it is only an impression, that in patients with heart failure that have auricular mural thrombi as a source of emboli, the infarcts are larger than those observed when the emboli arise from the leg veins. This certainly could be borne out in this case.

The liver was enlarged and showed a severe degree of central congestion. It is surprising that he did not develop jaundice with that degree of pulmonary infarction in addition to fairly severe liver disease.

There was about 200 to 300 cc. of straw-colored fluid in the right pleural cavity, and a similar amount on the left. I think it is surprising that one cannot see anything in the left lower lobe that suggests infarct. It measured 16 by 20 cm. at autopsy. Of course, it might well have occurred during the six days between death and the time this film was taken.

Dr. Myers: How old was the myocardial infarct?

Dr. Castleman: There were several areas of recent frank necrosis and also areas of granulation tissue. I believe that some foci of infarction could have been two months old.

Dr. Myers: Were the leg veins examined?

Dr. Castleman: Yes. At the time of operation no thrombi were found in the superficial femoral veins, and at autopsy the sites of the ligation were perfectly negative. Both profundas were examined and found free from thrombus. We did find a thrombus in the popliteal vein on the right, which I think occurred following ligation.

References

1. White, P. D. *Heart Disease.* Third edition. 1025 pp. New York: Macmillan Co., 1944.
2. Hampton, A. O., and Castleman, B. Correlation of postmortem chest teleroentgenograms with autopsy findings: with special reference to pulmonary embolism and infarction. *Am. J. Roentgenol.* **43**:305-326, 1940.

An index of the diagnoses and discussers of the Case Records for the year 1948 will be found elsewhere in this issue of the *Journal*.

The New England
Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established 1828

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY

OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE COMMITTEE ON PUBLICATIONS

Richard M. Smith, M.D., *Chairman*
James P. O'Hare, M.D. Conrad Wesselhoeft, M.D.
Oliver Cope, M.D. John Fallon, M.D.

Joseph Garland, M.D., EDITOR

ASSOCIATE EDITORS
Thomas H. Lanman, M.D. Donald Munro, M.D.
Henry Jackson, Jr., M.D.

Clara D. Davies, EXECUTIVE EDITOR
Robert O'Leary, ASSISTANT EDITOR

EDITORIAL BOARD
C. Guy Lane, M.D. Maxwell Finland, M.D.
Henry R. Viets, M.D. James M. Faulkner, M.D.
Robert M. Green, M.D. Carroll B. Larson, M.D.
Dwight O'Hara, M.D. Francis D. Moore, M.D.
Fletcher H. Colby, M.D. C. Stuart Welch, M.D.
Robert L. Goodale, M.D. Vernon P. Williams, M.D.
Chester M. Jones, M.D. Benjamin Castleman, M.D.
Harvey R. Morrison, M.D. Hugh R. Leavell, M.D.

SUBSCRIPTION TERMS: $7.00 per year in advance, postage paid, for the United States (medical students, $4.00 per year); Canada, $8.00 per year (Boston funds); $9.50 per year for all foreign countries belonging to the Postal Union.

MATERIAL should be received not later than noon on Thursday, three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS, *including those concerning classified advertising but not those regarding other advertising*, should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

NEW ENGLAND ADVERTISING REPRESENTATIVE (*except for classified advertising*): Edwin B. Tyler, 89 State Street, Boston, Massachusetts. Telephone LA 3-5516.

This issue has been prepared in two sections.

A NEW YEAR

HUMILITY, best defined by Webster as "freedom from pride and arrogance," may be of various types and may constitute the mask that hides a variety of underlying patterns. Among these types are the self-debasing humility of the uncompensated inferiority complex; the sinister pseudohumility that characterizes the Uriah Heeps; the arrogant humility of conscious rectitude as expressed in Burton's *Anatomy of Melancholy* — "They are proud in humility; proud in that they are not proud."

There is also the honest humility of true magnanimity, fearless because it makes no pretence, recognizing superior assets and capacities in others, acknowledging powers higher than those that humankind possesses, and admitting the likelihood that even the most capable person may sometimes be in error. It is a humility of the intellect, free from pride and arrogance.

One of the errors to which any person of ambition may be liable — and the higher his road is built the deeper are the ditches that flank it — is the development of a belief in his own infallibility. Too often a genuine call to service turns with the passage of time and under the influence of personal prestige into a sense of superiority over those served. Too frequently a long period of unchallenged leadership may betray the leader into a belief in the permanence of his own position; even in his inability to make the wrong judgment. Obsessed with this feeling of unassailable righteousness, he unconsciously assumes the mantle of perfection and with it something in the way of self-bestowed divinity. In his estimation of himself he has caught up with God.

Especially vulnerable to this particular loss of perspective are those who have been drawn into fields of activity in which personal influence is a strong factor. Among these are politicians with their constituents, writers with their readers, teachers with their pupils, pastors with their parishioners, physicians with their patients. A penalty attached to their sometime loss of humility, as expressed by an eminent preacher, is that they doubt God when it is themselves that they should doubt.

To them might be recalled the words of Cromwell to Parliament, the members of which he beseeched at one time to bear in mind that they "might be mistaken."

So for everyone a resolution with which to start a new year might be to bear in mind that he may be mistaken, that true humility is a virtue that can be cultivated, and that conscious and outspoken humility is its own contradiction.

MILESTONES

RELEASES from public-relations counsel at times seem like those from the butcher, replete with the lard of "significance" but shy of the lean of meaning. The copywriter's incomplete comparative is familiar: the better refrigerator, the better homes

and gardens, the better postwar automobiles. Better than what? Attention is now invited by a Detroit committee of the automobile industry to a "significant" milestone, the production of a hundred million motor vehicles. A significant milestone, it may be asked, on what road?

Since the first car, fifty-five years ago, production has been at an annual rate of nearly 2,000,000 vehicles until today more than 40,000,000 cars, trucks and busses crowd the nation's highways, one for every four persons in the United States. Every minute of each working day sees 30 new cars and 10 new trucks and busses. The second hundred millionth milestone should be reached in only twenty-five more years. This informative committee avers that research and mass production have cut costs and increased sales, and in turn have increased employment, raised the nation's standard of living and expanded retail trade areas; indeed, whole new industries dependent upon this new flexible transportation tool have been developed. Since the horseless-carriage tinkerers have come out of their alleys and quit selling bicycles, the labor, the ingenuity and the lives of millions of Americans have been absorbed in the making, selling and servicing of automobiles. Many thousands of other lives, it may be stated without exaggeration, have needlessly been sacrificed as a result of their labors.

Comment has been made on accidents as a leading cause of death.[1, 2] The all-time prewar record for deaths from automobile accidents was nearly 40,000 in 1941. Although in actual numbers heart disease and cancer are the primary killers, Dickinson and Welker[3] question the adequacy of numbers of deaths as the sole measure of the relative importance of the various causes. Two new measurements are suggested: "life years lost" and "working years lost." When the latter was applied to the seven leading causes of death in four five-year periods, 1930 to 1945, accident, as a destroyer of working years, was third in 1930, second in 1935 and first in 1940. In 1945, during gas rationing, the working years lost from accidental death numbered 1,750,000, whereas those from heart disease were 1,680,000. The young white man, representing the productive strength of the country, was the special victim. It is not implied that all, but only that too many, accidental deaths are due to the automobile. One hundred million cars, trucks and busses, and 40 more per minute! This significant milestone in the production line is also a marker on the broad way that leads to destruction.

Free enterprise and fierce competition within the industry, the committee believes, is responsible for this triumph of mass production. It is suggested, on the other hand, that the achievement marks a point on the errant road of reason. Since that fall day in 1793 when a popular actress was crowned goddess of reason in Notre Dame—and in spite of the bad consciences of Robespierre and others—the modern world has believed in and depended upon reason alone. In those early days revolutionary reason was most concerned with ends. The ends were utopian: truth, justice and enlightened self-interest would bring automatic harmony between individuals and society in nature. As absolutism and authoritarianism were crushed, new creative activity was released, bringing rapid advances in politics, economics, education and technics. With apparently complete success of republicanism and industrialism in the nineteenth century, revolutionary reason or the reason of ends was sacrificed to technical reason or the reason of means. This technical reason has produced the present large-scale, industrial, competitive, mass-producing economy rising above physical nature and man himself and its heretical counterpart the totalitarian state with its "planning reason."[4] The hundred millionth motor vehicle is the crown of technical knowledge.

This apogee of the assembly line, it is agreed, is a milestone of some sort. Yet 40,000 deaths a year is only a pace on the way of man against himself, since the atom bomb can do twice or three times as well in the twinkling of an eye. This record production of automobiles is a signal achievement on the road of technical reason, but this road remains the blind alley of men's hope. Nevertheless, whatever road it is, the automobile industry should be joined in their self-congratulation on their milestone. Let the public-relations counsel tot up the blessings of industrial culture at this season! One looks hopefully for a release from someone about a milestone,

however insignificant, on the straight and narrow path that leads to peace and good will among men.

References

1. Editorial. Leading causes of death. *New Eng. J. Med.* **239**:71, 1948.
2. Editorial. Public health and diseases of old age. *New Eng. J. Med.* **239**:487, 1948.
3. Medical Economics. What is leading cause of death? *J. A. M. A.* **138**: 528, 1948.
4. Tillich, P. J. World situation. In *Christian Answer.* Edited by H. P. Van Dusen. 195 pp. New York: Charles Scribner's Sons, 1946.

HANDKERCHIEFS AND THE TRANSFER OF RESPIRATORY INFECTIONS

"Don't put a cold in your pocket" is a slogan used by manufacturers of disposable tissues and designed to sell the public on the idea of substituting their product for the traditional handkerchief. The use of the latter, however, has long been thought to be an effective means of protecting others from infections. A sneeze or cough not protected by a handkerchief has been considered by many as tantamount to a direct assault on the health of one's neighbors — a sort of peacetime version of bacterial warfare. Some recent considerations of the possible role of the handkerchief in the spread of respiratory infections may provide further ammunition for the sales talks against the handkerchief although they offer little solace when it comes to the virtues of the tissues.

In one of the latest studies to be reported in this connection,[1] an estimate was made of the number of bacteria-carrying particles that can be shaken into the air from the handkerchiefs of people with and without nasal discharge. The average number of such particles in a series of 211 handkerchiefs was about 130,000. The particles were large enough to suggest that they each carried a number of bacteria. The predominant organism recovered was *Staphylococcus aureus* and corresponded with those found in cultures of nasal swabs or of the skin of the same subjects. In some cases nonhemolytic streptococci similar to those of the throat and mouth flora were found.

This study was carried out at the Harvard Hospital in England, where investigations are being conducted on the transmission of the common cold. Interestingly enough, there was but small difference between the average counts of infected particles shaken from the handkerchiefs of persons without nasal discharge and the counts of those with nasal discharge that was either slight, profuse or even purulent.

Because of the recent great interest in aerial disinfectants, studies were made of the effects of some of these agents on the bacteria shed from the handkerchiefs into the air. The infectious particles were found to be resistant to the action of several of the more potent of these aerial disinfectants, including ultraviolet rays and triethylene glycol, employed in the usual concentrations and at normal relative humidities.

Hamburger and Green[2] had previously called attention to the problem of the dangerous carriers of hemolytic streptococci when they found that large numbers of these bacteria could be recovered from the hands of nasal carriers. Hamburger[3] subsequently reported that literally hundreds of thousands of virulent hemolytic streptococci could frequently be recovered from the hands of such carriers. Furthermore, several hundred to almost 50,000 of these pathogens could be transferred to the hands of a noncarrier by an ordinary handshake. The greatest numbers were transferred by carriers who had just blown their noses into sterile handkerchiefs.

Although these experiments were not repeated with materials other than handkerchiefs, it is quite certain that the results would not have been very different had the subjects blown their noses into the best advertised of tissues and discarded them instead of using sterile handkerchiefs, which they would then have put into their pockets.

References

1. Dumbell, K. R., Lovelock, J. E., and Lowbury, E. J. Handkerchiefs in transfer of respiratory infection. *Lancet* **2**:183-185, 1948.
2. Hamburger, M., Jr., and Green, M. J. Problem of dangerous carrier of hemolytic streptococci. IV. Observations upon role of hands, of blowing nose, of sneezing, and of coughing in dispersal of microorganisms. *J. Infect. Dis.* **79**:33-44, 1946.
3. Hamburger, M., Jr. Transfer of beta hemolytic streptococci by shaking hands. *Am. J. Med.* **2**:23-25, 1947.

INFANT INVESTIGATOR

It is hard to realize that Dr. Arnold Gesell, after thirty-seven years on the Yale faculty, during most of which time he has been director of Yale's famous Clinic of Child Development, has retired — in order to expand his works still further. Some of Dr. Gesell's books, of which there are a full two dozen,

have been the vade mecum of the intellectual young mother, determined that she will rear only superior children. All of them, reporting on territory explored largely by their author, have been enlightening texts on infant behavior and books of reference for the pediatrician and the psychologist.

If one lesson only that Dr. Gesell taught were to be selected as his greatest contribution, it would be that each infant is a person, with its own appetites and satisfactions, its own capacities and its own built-in timing mechanism.

Dr. Gesell, now that he has demonstrated to the world all there is at present to know about child behavior (from the age of four months on), will continue his investigations at Yale University in charge of a child vision research project, under a grant from the American Optical Company. Those who have taken to heart the injunction that where there is no vision the people perish will rejoice that this work is to be under such able direction. Dr. Gesell's pupils, disciples and other fans will wish him continued success in his new work. They may perhaps, looking a long way back, be reminded of another investigator in better vision to whom has been given the credit for the invention of spectacles — Roger Bacon, the Dr. Mirabilis of his day.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CHANGES IN ISOLATION AND QUARANTINE REQUIREMENTS

The Department has recently made a number of changes in the list of reportable diseases and in the isolation and quarantine requirements. These changes will go into effect as soon as a printing of the revised regulations can be obtained and distribution made to boards of health, school departments, hospitals and other agencies.

To inform physicians of these changes, the following brief résumé is included in this column.

Infectious hepatitis has been added to the list of reportable diseases; hookworm disease, lobar pneumonia and suppurative conjunctivitis have been removed from the list.

Hereafter, there will be no differentiation in the handling of immune and nonimmune contacts of communicable diseases.

Poliomyelitis. The term "poliomyelitis" will be used instead of the former designation, "anterior poliomyelitis." This will change the order of the disease in the list and in the table of isolation and quarantine requirements. The deletion of the phrase "and thereafter until acute symptoms have subsided" leaves the isolation of the patient as a period of two weeks from the onset of the disease. All restrictions upon contacts, whether adults or children, have been removed. A placard will no longer be required for the disease.

Chancroid. There will be no restrictions upon contacts of this disease.

Chicken pox. The period of isolation will be seven days from the appearance of the eruption.

Diphtheria. The minimum time limit of one week for isolation of the patient has been eliminated. The patient will be isolated until clinical recovery and the obtaining of negative cultures. There will be no restrictions upon adult contacts of diphtheria, but child contacts will be excluded from school for one week after the patient has been hospitalized or until the child has lived away from home for one week.

Granuloma inguinale. There will be no restrictions upon contacts of patients with this disease.

Infectious hepatitis. Patients will be isolated for the duration of fever. There will be no restrictions upon contacts.

Leprosy. There will be no isolation of patients with leprosy.

Lymphogranuloma venereum. There will be no restrictions upon contacts of patients with this disease.

Meningitis, meningococcal. Patients will be isolated for only three days from the beginning of adequate sulfonamide therapy. There will be no restrictions upon contacts.

Meningitis, other forms. No isolation will be imposed upon cases of meningitis due to organisms other than the meningococcus.

Mumps. The patient with mumps will be isolated for a week from the onset of the disease, the reference to swelling of the salivary glands being eliminated from the regulations.

Ophthalmia neonatorum. Infants with infected eyes will be isolated only until two negative smears or cultures to rule out gonococcal ophthalmia have been obtained.

Salmonellosis. All paratyphoid infections will be included under this designation.

Plague. The new regulations place restrictions upon contacts of patients with plague only in pneumonic cases, in which the contacts are quarantined for seven days after the last exposure.

Scarlet fever. Isolation of both adults and children has been reduced to one week from appearance of the rash, and thereafter until clinically recovered, and until purulent discharges, if any, have ceased. Children may be allowed to go to school within one week after patient has been under adequate treatment, or the patient has been hospitalized.

Whooping cough. There will be no restrictions upon contacts of patients with whooping cough.

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The January schedule for Consultation Clinics for Crippled Children in Massachusetts under the provisions of the Social Security Act follows:

Clinic	Date	Clinic Consultant
Salem	January 3	Paul W. Hugenberger
Haverhill	January 5	William T. Green
Lowell	January 7	Albert H. Brewster
Greenfield	January 10	Charles L. Sturdevant
Gardner	January 11	Carter R. Rowe
Brockton	January 13	George W. Van Gorder
Springfield	January 18	Garry deN. Hough, Jr.
Pittsfield	January 19	Frank A. Slowick
Hyannis	January 20	Paul L. Norton
Worcester	January 21	John W. O'Meara
Fall River	January 24	David S. Grice

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

CORRESPONDENCE

A CORRECTION

To the Editor: In an excellent review of the book *Hodgkin's Disease and Allied Diseases* by Parker and Jackson in the December 2 issue of the *Journal* there are two factual errors. The review is clearly written by a man of experience and knowledge so that these errors may easily have slipped into the preparation of the manuscript. Nevertheless, I believe that they should be corrected. In the review it is stated that we suggest dropping the term endothelioma, which was not intended. We *do* require a complete autopsy before such a diagnosis is made, for endothelioma, frequent in Java, may very closely simulate undifferentiated carcinoma and unless this condition can be ruled out we believe a diagnosis of endothelioma is unwise. Secondly, the reviewer, though twice using the term giant-follicle lymphoma, once refers to giant-follicle lymphosarcoma. In our opinion "giant-follicle lymphosarcoma" does not and, indeed, cannot exist, even though practically all students of the subject agree that giant-follicle lymphoma frequently progresses, with the passage of time, into lymphosarcoma. The diagnosis, treatment and prognosis is then that of the latter condition — lymphosarcoma.

Henry Jackson, Jr., M.D.
Mallory Institute of Pathology
Boston City Hospital

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

History of the Medical Society of the District of Columbia. Part II, 1833-1944. History Committee: John Benjamin Nichols, chairman, William Johnston Mallory and Joseph Stiles Wall. 8°, cloth, 357 pp., with 13 illustrations and frontispiece. Baltimore: Waverley Press, Incorporated, 1947.

This second volume of the history of the Society continues the narrative to approximately July 1, 1944. All the activities of the Society are covered, and a list of members from 1833 to 1911 is appended to the text. Two indexes with subjects and personal names conclude the volume. The book is well published and is recommended for history of medicine collections.

Gardiner's Handbook of Skin Diseases. Revised by John Kinnear, O.B.E., T.D., M.D., M.R.C.P. (Ed.), D.L., lecturer in diseases of the skin, St. Andrews University, physician for diseases of the skin, Dundee Royal Infirmary, and dermatologist, pre-school and school medical services, Dundee. Fifth edition. 12°, cloth, 250 pp., with 80 illustrations and colored plates. Baltimore: The Williams and Wilkins Company, 1948. $4.50.

This fifth edition of a popular manual, first printed in 1919, has been revised to bring it up to date since the printing of the third edition in 1939. The text was printed in Great Britain and bound in the United States. The volume reflects the British aspect of dermatology.

The Year Book of Pathology and Clinical Pathology. "Pathology," editor, Howard T. Karsner, M.D., professor of pathology, director of the Institute of Pathology, Western Reserve University, Cleveland; assistant editor, Herbert Z. Lund, M.D., assistant professor of pathology, Western Reserve University, Cleveland. "Clinical Pathology," editor, Arthur H. Sanford, M.D., professor of clinical pathology, University of Minnesota (The Mayo Foundation), and senior consultant, Division of Clinical Laboratories, Mayo Clinic. 12°, cloth, 558 pp., with 102 illustrations. Chicago: The Year Book Publishers, Incorporated, 1948. $3.75.

The Year Book of Pathology ceased publication in 1941 because of war and post-war conditions. It has now been reissued, and the present volume abstracts the literature for the year 1947. The volume is well published and is recommended for all medical libraries and to persons interested in the subject.

Ophthalmology in the War Years. Edited by Meyer Wiener, M.D., professor of clinical ophthalmology, Washington University School of Medicine, and honorary consultant in ophthalmology, Bureau of Medicine and Surgery, United States Navy. Volume II (1944-June, 1946). 8°, cloth, 997 pp. Chicago: The Year Book Publishers, Incorporated, 1948. $16.00.

This second volume attempts to include in the reviews everything of importance published during the period of two and a half years from 1944 to June, 1946. Thirty-seven persons have contributed to the volume. A few chapters not in the first volume have been added to make the work complete and up to date. Articles not discussed in the reviews have been listed in the bibliographies appended to the chapters. Comprehensive indexes of subjects and authors conclude the volume. The type and paper are good, and the printing excellent. The work is recommended for all medical libraries and ophthalmologists.

Essentials of Fevers. By Gerald E. Breen, M.D., B.Ch. (N.U.I. Dub.), D.P.H., D.O.M.S. (R.C.P. Lond., R.C.S. Eng.). Second edition. 16°, cloth, 351 pp., with 23 illustrations and 17 plates. Baltimore: The Williams and Wilkins Company, 1948. $4.50.

This second edition of a manual, first published in 1939, has been revised to include new sections on typhus, glandular and undulant fevers, influenza and encephalitis lethargica. Additions have been made to the chapters on sore throat and food poisoning. The article on dysentery has been rewritten and expanded. Color plates have been included for the first time. The type, printing and paper are good (the book was printed in Great Britain). The manual should prove useful as a reference source for the general practitioner.

Conference on Metabolic Aspects of Convalescence. Transactions of the fifteenth meeting. Edited by Edward C. Reifenstein, Jr., M.D. 8°, paper, 163 pp., with 35 illustrations. New York: Josiah Macy, Jr. Foundation, 1947. $2.25.

This conference was featured by a symposium on the isotopes with fourteen persons participating. Eighteen other persons contributed discussions on various aspects of metabolism. The different conferences of the Macy Foundation should be in all medical libraries.

NOTICES

JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

30 Bennet Street, Boston
Lecture Hall, 9-10 a.m.

MEDICAL CONFERENCE PROGRAM

Tuesday, January 4 — Vitamin B_{12} Therapy in Pernicious Anemia. Dr. Abraham Frumin.

Friday, January 7 — Carcinoma of the Cervix. Dr. Howard Ulfelder.

Wednesday, January 12 — Pediatric Clinicopathological Conference. Drs. James M. Baty and H. E. MacMahon.

Friday, January 14 — Differential Spinal Block. Dr. Stanley J. Sarnoff.

Tuesday, January 18 — *Journal* review.

Friday, January 21 — Simplified Blood Sugar Screening Method. Dr. Hugh L. C. Wilkerson.

Tuesday, January 25 — The Clinical Use of Washed Red Cell Transfusions. Dr. Jacob Neber.

Friday, January 28 — The Use of Tests that Measure Hepatic Excretory Functions. Dr. Albert I. Mendeloff.

On Tuesday morning, January 11, from 9 to 10 o'clock and on Wednesday mornings, January 5, 19 and 26, from 9 to 10 o'clock, Dr. S. J. Thannhauser will give medical clinics on hospital cases. On Thursday mornings from 9 to 10 o'clock clinics will be given by Dr. William Dameshek.

On the second and fourth Fridays of the month, January 14 and 28, therapeutic conferences will be held with round-table discussion from 2 to 4 o'clock (Dr. Robert P. McCombs, moderator). On the second and fourth Fridays, January 14 and 28, Dr. Merrill Sosman will conduct x-ray conferences from 4 to 6 o'clock. On Saturday mornings from 9 to 10 o'clock surgical clinics will be given by Dr. C. Stuart Welch. Medical rounds are conducted each weekday except Saturday by members of the hospital staff from 12 to 1 o'clock.

All exercises are open to the medical profession.

NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, January 6, at 7:15 p.m. in the classroom of the Nurses' Residence. Dr. Cleaveland Floyd will speak on the subject "Miliary Tuberculosis." Dr. Pauline Luzackas will be chairman.

NEW ENGLAND HEART ASSOCIATION

A meeting of the New England Heart Association will be held in the amphitheater of the Dowling Building, Boston City Hospital, on Monday, January 10, at 8:15 p.m., Dr. Laurence B. Ellis presiding.

PROGRAM

Functional Renal Insufficiency Precipitated in Patients with Congestive Failure by Sodium Depletion. Drs. Frank Drinan and Kermit H. Katz.

Mitral Stenosis, with Special Reference to Surgical Intervention.

Clinical-Physiologic Correlations. Drs. Laurence B. Ellis, J. G. Mebane, George Maresh, W. K. Long, and R. A. Bloomfield.

Experimental Studies on Mitral-Valve Function. Dr. Leona R. Norman.

Surgical Aspects. Dr. Dwight E. Harken.

Thrombosis in Arteriosclerosis of the Lower Extremities. Dr. Edward A. Edwards.

Interested physicians and medical students are cordially invited to attend.

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

A meeting of the New England Society of Anesthesiologists will be held in the Auditorium of Building A, Boston University School of Medicine, 80 East Concord Street, Boston, on Tuesday, January 11, at 8:00 p.m. The scientific program will consist of the following:

Changes in Body Fluid Chemistry as They Affect Preoperative and Postoperative Care. Francis D. Moore, M.D.

The Clinical Aspects of Pulmonary Atelectasis. Cutting B. Favour, M.D.

Pathologic Aspects of Postoperative Pulmonary Atelectasis. Joseph D. Boggs, M.D.

Aspiration Bronchoscopy in the Treatment of Postoperative Pulmonary Atelectasis. William S. Derrick, M.D.

Physicians and medical students are invited.

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the amphitheater of Building D, Harvard Medical School, on Tuesday, January 11 at 8:00 p.m. The chairman for the evening is Dr. Raymond D. Adams.

PROGRAM

The Correlation between Morphologic and Functional Disorders in the Motor-Nerve Cells in Poliomyelitis. Derek E. Denny-Brown and Joseph M. Foley.

An Encephalomyelitic Virus of Mice Causing Demyelinating Lesions of the Central Nervous System. F. Sargent Cheever, O. T. Bailey and A. M. Pappenheimer.

Pathological Changes in Carbon Monoxide Poisoning. Charles S. Kubik.

Subsequent meetings will be held on February 8, March 8, April 12 and May 10.

SUFFOLK DISTRICT MEDICAL SOCIETY

The third medicolegal meeting of the Suffolk District Medical Society and the Boston Bar Association will be held in Ware Hall, Boston Medical Library, on Wednesday, January 12, at 8 p.m. Dr. Alan R. Moritz will speak on the subject "Scientific and Medical Tests in Legal Proceedings," which will be discussed by Mr. Arthur F. Bickford, prominent Boston trial lawyer.

NEW ENGLAND PEDIATRIC SOCIETY

The annual meeting of the New England Pediatric Society will be held on Wednesday, January 26.

After the business meeting of the evening, Dr. Bronson Crothers will speak on the subject, "The Position of the Pediatrician in Relation to Specialists of Various Categories, Present and Impending."

Further details concerning the meeting will be forthcoming at a later date.

UNIVERSITY OF WISCONSIN SYMPOSIUM ON SCIENCE AND CIVILIZATION

As part of the general celebration of the centennial anniversary of the University of Wisconsin, the University's History of Science Group is sponsoring a symposium on "Science and Civilization." This symposium will be held January 13-15 at the Memorial Union of the University of Wisconsin in Madison.

MISSISSIPPI VALLEY MEDICAL SOCIETY

The annual meeting of the Mississippi Valley Medical Society will be held at the Jefferson Hotel, St. Louis, Missouri, from September 28 to 30, under the presidency of Dr. Alphonse McMahon, of St. Louis University.

(Notices concluded on page vii)